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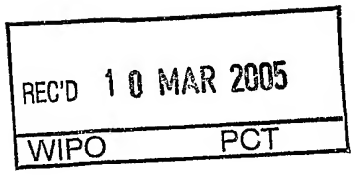

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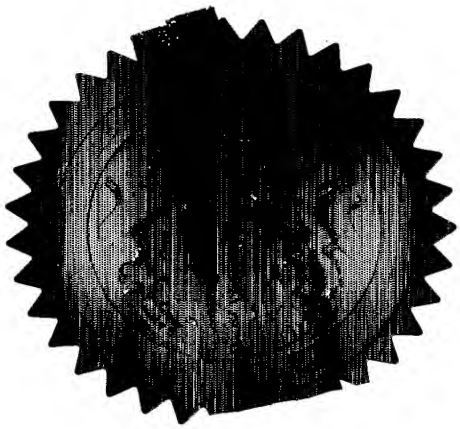
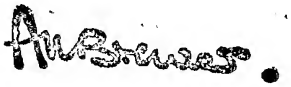


Signed 

Dated 20 January 2005

16JUN04 E903869-2 D02934
P01/7700 0.00-0413388.0 NONE

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The Patent Office

Cardiff Road
Newport
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NP10 8QQ

1. Your reference — 101380-2

2. Patent application number
(The Patent Office will fill in this part) — 0413388.0 — 16 JUN 2004

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* 78224 8003

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention

COMPOUNDS

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca
Global Intellectual Property
P O Box 272
Mereside, Alderley Park
Macclesfield,
Cheshire SK10 4GR

Patents ADP number *(if you know it)* 81797007001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	82
Claim *(s)*	5
Abstract	
Drawing *(s)*	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature S. A. Douglas Date 15/06/2004

12. Name and daytime telephone number of person to contact in the United Kingdom: Shirley Douglas 01625 510057

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COMPOUNDS

The present invention relates to a group of benzoyl amino heterocyclyl compounds which are useful in the treatment or prevention of a disease or medical condition mediated through glucokinase (GLK or GK), leading to a decreased glucose threshold for insulin secretion. In addition the compounds are predicted to lower blood glucose by increasing hepatic glucose uptake. Such compounds may have utility in the treatment of Type 2 diabetes and obesity. The invention also relates to pharmaceutical compositions comprising said compounds and to methods of treatment of diseases mediated by GLK using said compounds.

In the pancreatic β-cell and liver parenchymal cells the main plasma membrane glucose transporter is GLUT2. Under physiological glucose concentrations the rate at which GLUT2 transports glucose across the membrane is not rate limiting to the overall rate of glucose uptake in these cells. The rate of glucose uptake is limited by the rate of phosphorylation of glucose to glucose-6-phosphate (G-6-P) which is catalysed by glucokinase (GLK) [1]. GLK has a high (6-10mM) Km for glucose and is not inhibited by physiological concentrations of G-6-P [1]. GLK expression is limited to a few tissues and cell types, most notably pancreatic β-cells and liver cells (hepatocytes) [1]. In these cells GLK activity is rate limiting for glucose utilisation and therefore regulates the extent of glucose induced insulin secretion and hepatic glycogen synthesis. These processes are critical in the maintenance of whole body glucose homeostasis and both are dysfunctional in diabetes [2].

In one sub-type of diabetes, Maturity-Onset Diabetes of the Young Type 2 (MODY-2), the diabetes is caused by GLK loss of function mutations [3, 4]. Hyperglycaemia in MODY-2 patients results from defective glucose utilisation in both the pancreas and liver [5]. Defective glucose utilisation in the pancreas of MODY-2 patients results in a raised threshold for glucose stimulated insulin secretion. Conversely, rare activating mutations of GLK reduce this threshold resulting in familial hyperinsulinism [6, 6a, 7]. In addition to the reduced GLK activity observed in MODY-2 diabetics, hepatic glucokinase activity is also decreased in type 2 diabetics [8]. Importantly, global or liver selective overexpression of GLK prevents or reverses the development of the diabetic phenotype in both dietary and genetic models of the disease [9-12]. Moreover, acute treatment of type 2 diabetics with fructose improves glucose tolerance through stimulation of hepatic glucose utilisation [13]. This effect is believed to be

mediated through a fructose induced increase in cytosolic GLK activity in the hepatocyte by the mechanism described below [13].

Hepatic GLK activity is inhibited through association with GLK regulatory protein (GLKRP). The GLK/GLKRP complex is stabilised by fructose-6-phosphate (F6P) binding to the GLKRP and destabilised by displacement of this sugar phosphate by fructose-1-phosphate (F1P). F1P is generated by fructokinase mediated phosphorylation of dietary fructose. Consequently, GLK/GLKRP complex integrity and hepatic GLK activity is regulated in a nutritionally dependent manner as F6P is dominant in the post-absorptive state whereas F1P predominates in the post-prandial state. In contrast to the hepatocyte, the pancreatic β-cell expresses GLK in the absence of GLKRP. Therefore, β-cell GLK activity is regulated extensively by the availability of its substrate, glucose. Small molecules may activate GLK either directly or through destabilising the GLK/GLKRP complex. The former class of compounds are predicted to stimulate glucose utilisation in both the liver and the pancreas whereas the latter are predicted to act exclusively in the liver. However, compounds with either profile are predicted to be of therapeutic benefit in treating Type 2 diabetes as this disease is characterised by defective glucose utilisation in both tissues.

GLK, GLKRP and the K_{ATP} channel are expressed in neurones of the hypothalamus, a region of the brain that is important in the regulation of energy balance and the control of food intake [14-18]. These neurones have been shown to express orectic and anorectic neuropeptides [15, 19, 20] and have been assumed to be the glucose-sensing neurones within the hypothalamus that are either inhibited or excited by changes in ambient glucose concentrations [17, 19, 21, 22]. The ability of these neurones to sense changes in glucose levels is defective in a variety of genetic and experimentally induced models of obesity [23-28]. Intracerebroventricular (icv) infusion of glucose analogues, that are competitive inhibitors of glucokinase, stimulate food intake in lean rats [29, 30]. In contrast, icv infusion of glucose suppresses feeding [31]. Thus, small molecule activators of GLK may decrease food intake and weight gain through central effects on GLK. Therefore, GLK activators may be of therapeutic use in treating eating disorders, including obesity, in addition to diabetes. The hypothalamic effects will be additive or synergistic to the effects of the same compounds acting in the liver and/or pancreas in normalising glucose homeostasis, for the treatment of Type 2 diabetes. Thus the GLK/GLKRP system can be described as a potential "Diabesity" target, i.e. beneficial in both Diabetes and Obesity.

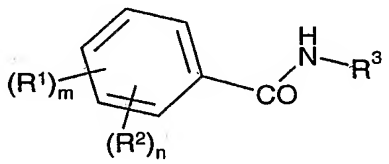
GLK is also expressed in specific entero-endocrine cells where it is believed to control the glucose sensitive secretion of the incretin peptides GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (Glucagon-Like Peptide-1) from gut K-cells and L-cells respectively (32, 33, 34). Therefore, small molecule activators of GLK may have additional beneficial effects on insulin secretion, b-cell function and survival and body weight as a consequence of stimulating GIP and GLP-1 secretion from these entero-endocrine cells.

In WO00/58293 and WO01/44216 (Roche), a series of benzylcarbamoyl compounds are described as glucokinase activators. The mechanism by which such compounds activate GLK is assessed by measuring the direct effect of such compounds in an assay in which GLK activity is linked to NADH production, which in turn is measured optically - see details of the *in vitro* assay described hereinafter. Compounds of the present invention may activate GLK directly or may activate GLK by inhibiting the interaction of GLKRP with GLK.

Further GLK activators have been described in WO03/095438 (substituted phenylacetamides, Roche), WO03/055482 (carboxamide and sulphonamide derivatives, Novo Nordisk), WO2004/002481 (arylcarbonyl derivatives, Novo Nordisk), and in WO03/080585 (amino-substituted benzoylaminoheterocycles, Banyu).

Our International application Number: WO03/000267 describes a group of benzoyl amino pyridyl carboxylic acids which are activators of the enzyme glucokinase (GLK).

Our International application Number: WO03/015774 describes compounds of the Formula (A):



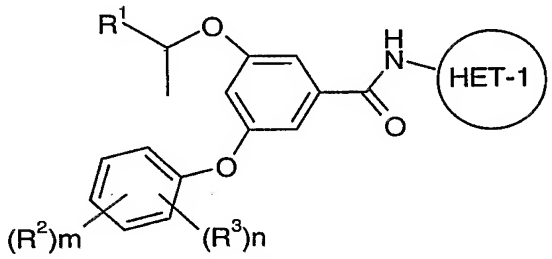
(A)

wherein R^3 is a substituted heterocycle, and wherein the substituents R^1, R^2 and those on the heterocycle R^3 are selected such that the compounds are overall neutral.

We have surprisingly found a small group of compounds, generally a selected subgroup of those described in WO 03/015774, which have generally superior potency for the GLK enzyme, and more advantageous physical properties, including, for example, higher aqueous solubility, higher permeability, and/or lower plasma protein binding. Consequently, such compounds would be expected to display higher plasma free drug levels and superior in vivo efficacy after oral dosing as determined, for example, by activity in Oral Glucose

Tolerance Tests (OGTTs). Therefore this group of compounds would be expected to provide superior oral exposure at a lower dose and thereby be particularly suitable for use in the treatment or prevention of a disease or medical condition mediated through GLK.

Thus, according to the first aspect of the invention there is provided a compound of Formula (I):



(I)

wherein:

R^1 is methyl;

R^2 is selected from $-C(O)NR^4R^5$, $-SO_2NR^4R^5$, $-S(O)_pR^4$ and HET-2;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 4-, 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring may optionally be oxidised to an S(O) or $S(O)_2$ group, which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano;

R^4 is selected from hydrogen, (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$] and HET-2;

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a heterocyclyl ring system as defined by HET-2;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4;

R^7 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to an S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an N-linked, 7 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further heteroatom (in addition to the linking N atom) independently selected from O, S and N, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- group and wherein a sulphur atom in the ring may optionally be oxidised to an S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an 6-10 membered bicyclic saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further nitrogen atom (in addition to the linking N atom), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-; which ring is optionally substituted on an available carbon or nitrogen atom by 1 substituent selected from R^3;

R^8 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkylamino, di(1-4C)alkylamino, HET-3 (wherein said ring is unsubstituted), (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-4 is a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S;

p is (independently at each occurrence) 0, 1 or 2;

m is 0 or 1;

n is 0, 1 or 2;

provided that when m is 0, then n is 1 or 2;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention there is provided a compound of the formula (I), or a salt, pro-drug or solvate thereof, wherein:

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8.

It will be understood that when R^4 is $-C(O)NR^5R^5$, each R^5 is independently selected from hydrogen and (1-4C)alkyl, and therefore this definition of R^4 includes (but is not limited to) $-CONH_2$, -CONHMe, $-CONMe_2$ and –CONMeEt.

It will be understood that where a compound of the formula (I) contains more than one HET-2 ring, they may be the same or different.

It will be understood that where a compound of the formula (I) contains more than one group R^4, they may be the same or different.

It will be understood that where a compound of the formula (I) contains more than one group R^5, they may be the same or different.

It will be understood that where a compound of the formula (I) contains more than one group R^8, they may be the same or different.

A similar convention applies for all other groups and substituents on a compound of formula (I) as hereinbefore defined.

Compounds of Formula (I) may form salts which are within the ambit of the invention. Pharmaceutically acceptable salts are preferred although other salts may be useful in, for example, isolating or purifying compounds.

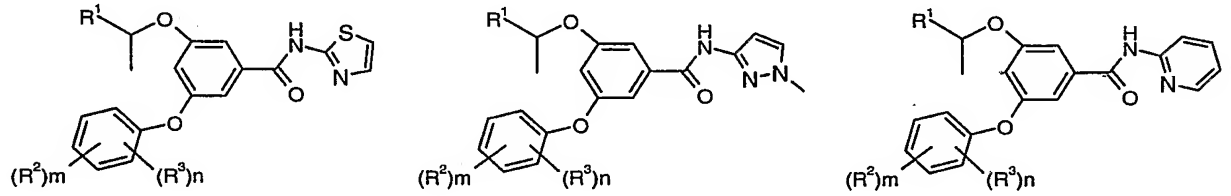
In another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to a pharmaceutically acceptable salt.

In another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to a pro-drug thereof. Suitable examples of pro-drugs of compounds of formula (I) are in-vivo hydrolysable esters of compounds of formula (I). Therefore in another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to an in-vivo hydrolysable ester thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only and references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. For example,

"(1-4C)alkyl" includes methyl, ethyl, propyl, isopropyl and *t*-butyl. An analogous convention applies to other generic terms.

For the avoidance of doubt, reference to the group HET-1 containing a nitrogen in the 2-position, is intended to refer to the 2-position relative to the amide nitrogen atom to which the group is attached. For example, the following structures are encompassed (but not limited to):



Suitable examples of HET-1 as a 5- or 6-membered, C-linked heteroaryl ring as hereinbefore defined, include thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, tetrazolyl and triazolyl.

It will be understood that HET-2 can be a saturated, or partially or fully unsaturated ring.

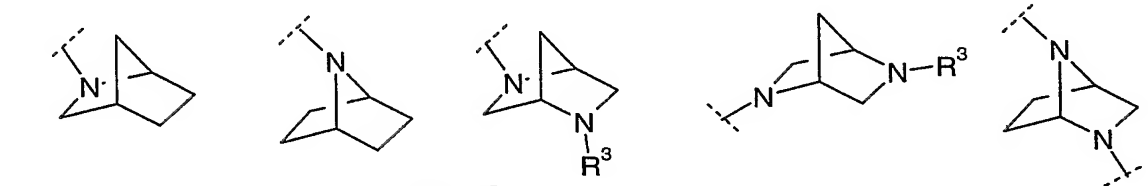
Suitable examples of HET-2 include azetidinyl, furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, morpholino, morpholinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, 2-oxo-1,3,4-(4-triazolinyl), 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 1,2,4-triazolyl, 1,2,3-triazolyl, pyranyl, and 4-pyridonyl.

It will be understood that HET-2 may be linked by any appropriate available C or N atom, therefore for example, for HET-2 as "imidazolyl" includes 1- , 2-, 4- and 5- imidazolyl.

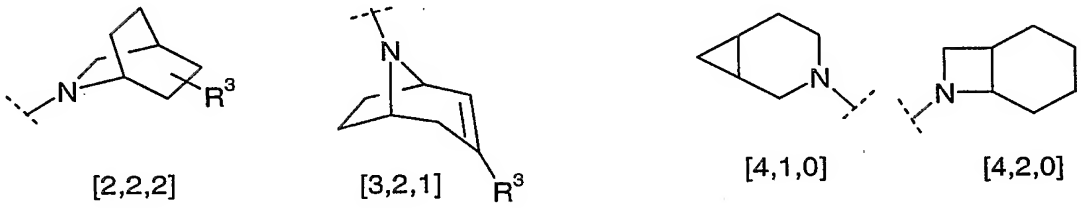
Suitable examples of HET-3 as a 4-6 membered saturated or partially unsaturated heterocyclic ring are morpholino, piperidinyl, piperazinyl, pyrrolidinyl and azetidinyl.

Suitable examples of HET-3 as a 7-membered saturated or partially unsaturated heterocyclic ring are homopiperazinyl, homo-morpholino, homo-thiomorpholino (and versions thereof wherein the sulfur is oxidised to an SO or $S(O)_2$ group) and homo-piperidinyl.

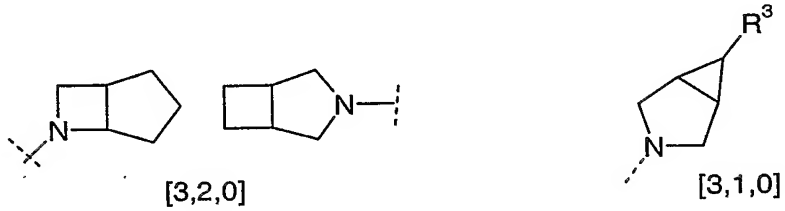
Suitable examples of HET-3 as an 6-10 membered bicyclic heterocyclic ring are bicyclic saturated or partially unsaturated heterocyclyl ring such as those illustrated by the structures shown below (wherein the dotted line indicates the point of attachment to the rest of the molecule):



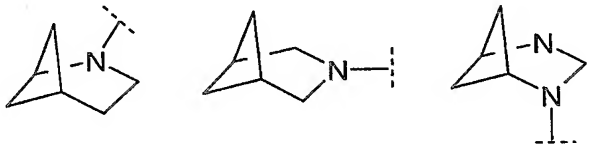
[2,2,1]



[2,2,2] [3,2,1] [4,1,0] [4,2,0]



[3,2,0] [3,1,0]



[3,1,1]

Suitable examples of HET-3 are morpholino, piperidinyl, piperazinyl, pyrrolidinyl and azetidinyl.

Suitable examples of HET-4 are furyl, pyrrolyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl and triazolyl.

It will be appreciated that, where definitions of heterocylyl groups HET-1 to HET-4 encompass heteroaryl rings which may be substituted on nitrogen, such substitution may not result in charged quaternary nitrogen atoms. It will be appreciated that the definitions of HET-1 to HET-4 are not intended to include any O-O, O-S or S-S bonds. It will be appreciated that the definitions of HET-1 to HET-4 are not intended to include unstable structures.

Examples of **(1-4C)alkyl** include methyl, ethyl, propyl, isopropyl, butyl and tert-butyl; examples of **(3-6C)cycloalkyl** include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; examples of **halo** include fluoro, chloro, bromo and iodo; examples of **hydroxy(1-4C)alkyl** include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxyisopropyl and 4-hydroxybutyl; examples of **(1-4C)alkoxy(1-4C)alkyl** include methoxymethyl, ethoxymethyl, tert-butoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, methoxypropyl, 2-methoxypropyl and methoxybutyl; examples of **(1-4C)alkylS(O)p(1-4C)alkyl** include methylsulfinylmethyl, ethylsulfinylmethyl, ethylsulfinylethyl, methylsulfinylpropyl, methylsulfinylbutyl, methylsulfonylmethyl, ethylsulfonylmethyl, ethylsulfonylethyl, methylsulfonylpropyl, methylsulfonylbutyl, methylthiomethyl, ethylthiomethyl, ethylthioethyl, methylthiopropyl, and methylthiobutyl; examples of **amino(1-4C)alkyl** include aminomethyl, aminoethyl, 2-aminopropyl, 3-aminopropyl, 1-aminoisopropyl and 4-aminobutyl; examples of **(1-4C)alkylamino(1-4C)alkyl** include (N-methyl)aminomethyl, (N-ethyl)aminomethyl, 1-((N-methyl)amino)ethyl, 2-((N-methyl)amino)ethyl, (N-ethyl)aminoethyl, (N-methyl)aminopropyl, and 4-((N-methyl)amino)butyl; examples of **di(1-4C)alkylamino(1-4C)alkyl** include dimethylaminomethyl, methyl(ethyl)aminomethyl, methyl(ethyl)aminoethyl, (N,N-diethyl)aminoethyl, (N,N-dimethyl)aminopropyl and (N,N-dimethyl)aminobutyl; examples of **(1-4C)alkylamino** include methylamino, ethylamino, propylamino, isopropylamino, butylamino and tert-butylamino; examples of **di(1-4C)alkylamino** include dimethylamino, methyl(ethyl)amino, diethylamino, dipropylamino, di-isopropylamino and dibutylamino; examples of **–C(O)(1-4C)alkyl** include methylcarbonyl, ethylcarbonyl, propylcarbonyl and tert-butyl carbonyl.

It is to be understood that, insofar as certain of the compounds of Formula (I) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of stimulating GLK directly or inhibiting the GLK/GLKRP interaction. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. It is also to be understood that certain

compounds may exist in tautomeric forms and that the invention also relates to any and all tautomeric forms of the compounds of the invention which activate GLK.

In one embodiment of the invention are provided compounds of formula (I), in an alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (I), in a further alternative embodiment are provided in-vivo hydrolysable esters of compounds of formula (I), and in a further alternative embodiment are provided pharmaceutically-acceptable salts of in-vivo hydrolysable esters of compounds of formula (I).

Particular values of variable groups are as follows. Such values may be used where appropriate with any of the values, definitions, claims, aspects or embodiments defined hereinbefore or hereinafter.

(1) R^2 is $-C(O)NR^4R^5$

(2) R^2 is $-SO_2NR^4R^5$

(3) R^2 is $-S(O)_pR^4$

(4) R^2 is HET-2

(5) m is 1 and R^2 is in the para position relative to the ether linkage

(6) m is 1 and n is 0 or 1

(7) m is 1 and n is 0

(8) m is 1, n is 0 and R^2 is in the para position relative to the ether linkage

(9) n is 0

(10) n is 1

(11) n is 2

(12) n is 2 and both R^3 are halo

(13) R^3 is halo or trifluoromethyl

(14) R^3 is halo

(15) R^3 is chloro or fluoro

(16) R^3 is fluoro

(17) n is 2 and both R^3 are fluoro,

(18) n is 2, both R^3 are fluoro and are in the 3- and 5-positions relative to the ether linkage

(19) p is 0

(20) p is 1

(21) p is 2

[illegible]

(23) HET-1 is a 6-membered heteroaryl ring

(24) HET-1 is substituted with 1 or 2 substituents independently selected from R^6

(25) HET-1 is substituted with 1 substituent selected from R^6

(26) HET-1 is unsubstituted

(27) HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, and triazolyl

(28) HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl

(29) HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl

(30) HET-1 is selected from thiazolyl, pyrazolyl and oxazolyl

(31) HET-1 is selected from thiadiazolyl and oxadiazolyl

(32) HET-1 is selected from 1,3,4-thiadiazolyl and 1,3,4-oxadiazolyl

(33) HET-1 is selected from 1,2,4-oxadiazolyl and 1,2,4-oxadiazolyl

(34) HET-1 is pyridyl

(35) HET-1 is pyrazinyl

(36) R^6 is selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4

(37) R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, dimethylaminomethyl

(38) R^6 is selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, and di(1-4C)alkylamino(1-4C)alkyl

(39) R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl

(40) R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl and methoxymethyl

(41) R^6 is selected from methyl, ethyl, bromo, chloro and fluoro

(42) R^6 is methyl

(43) R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, dimethylaminomethyl, hydroxymethyl and methoxymethyl

(44) when 2 substituents R^6 are present, both are selected from methyl, ethyl, bromo, chloro and fluoro, preferably both are methyl

(45) HET-4 is selected from furyl, pyrrolyl and thienyl

(46) HET-4 is furyl

(47) R^4 is hydrogen

(48) R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$]

(49) R^4 is (1-4C)alkyl [optionally substituted by 1 substituent selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$]

(50) R^4 is HET-2

(51) R^4 is selected from hydrogen, (1-4C)alkyl, and (1-4C)alkyl substituted with $-OR^5$

(52) HET-2 is unsubstituted

(53) HET-2 is substituted with 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy and (1-4C)alkoxy

(54) HET-2 is a fully saturated ring system

(55) HET-2 is a fully unsaturated ring system

(56) HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl

(57) HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, thiomorpholinyl, tetrahydrofuranyl, and tetrahydropyranyl

(58) HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl

(59) HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, pyrrolidonyl, 2-oxazolidinonyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl

(60) HET-2 is selected from morpholino, furyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, 2-pyrrolidonyl, 2-oxazolidinonyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl and 2-oxoimidazolidinyl

(61) HET-2 is selected from morpholino, furyl, imidazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, 2-pyrrolidonyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl

(62) R^5 is hydrogen

(63) R^5 is (1-4)alkyl

(64) R^5 is hydrogen or methyl

(65) R^7 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkoxy(1-4C)alkyl, and hydroxy(1-4C)alkyl

(66) R^7 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, and hydroxy(1-4C)alkyl

(67) R^7 is selected from hydroxy, methoxy, -COMe, $-CONH_2$, -CONHMe, $-CONMe_2$, and hydroxymethyl

(68) R^7 is selected from (1-4C)alkyl, hydroxy and (1-4C)alkoxy

(69) R^7 is selected from methyl, ethyl, methoxy and hydroxy

(70) R^8 is selected from methyl, hydroxy, methoxy, -COMe, $-CONH_2$, -CONHMe, $-CONMe_2$, hydroxymethyl, hydroxyethyl, -NHMe and $-NMe_2$(71) R^8 is selected from morpholino, piperidinyl, piperazinyl, pyrrolidinyl and azetidinyl

(72) R^8 is selected from methyl, -COMe, $-CONH_2$, hydroxyethyl and hydroxy

(73) HET-3 is a fully saturated ring

(74) HET-3 is selected from morpholino, piperidinyl, piperazinyl, pyrrolidinyl and azetidinyl

(75) R^4 and R^5 together with the nitrogen to which they are attached form a ring as defined by HET-3

(76) HET-3 is a 4 to 6-membered saturated or partially unsaturated heterocyclic ring

(77) HET-3 is a 7-membered saturated or partially unsaturated heterocyclic ring

(78) HET-3 is an 6 to 10-membered bicyclic saturated or partially unsaturated heterocyclic ring

According to a further feature of the invention there is provided the following preferred groups of compounds of the invention:

In a futher aspect of the invention there is provided a compound of Formula (I) wherein:

R^1 is methyl;

R^2 is selected from $-C(O)NR^4R^5$, $-SO_2NR^4R^5$, $-S(O)_pR^4$ and HET-2;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1, 2 or 3 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring may optionally be oxidised to an S(O) or $S(O)_2$ group, which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano;

R^4 is selected from hydrogen, (1-4C)alkyl [optionally substituted by $-OR^5$] and HET-2;

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a 4-6 membered heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4;

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein sulphur atoms in the ring may optionally be oxidised to S(O) or $S(O)_2$ groups; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8;

R^8 is selected from $-OR^5$ and (1-4C)alkyl;

HET-4 is a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S;

p is (independently at each occurrence) 0, 1 or 2;

m is 0 or 1;

n is 0, 1 or 2.

provided that when m is 0, then n is 1 or 2;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention there is provided a compound of Formula (I) wherein:

R^1 is methyl;

R^2 is selected from $-C(O)NR^4R^5$, $-SO_2NR^4R^5$, $-S(O)_pR^4$ and HET-2;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1, 2 or 3 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring may optionally be oxidised to an S(O) or $S(O)_2$ group, which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano;

R^4 is selected from hydrogen, (1-4C)alkyl [optionally substituted by $-OR^5$] and HET-2;

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a 4-6 membered heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4;

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to an S(O) or

$S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an N-linked, 7 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further heteroatom (in addition to the linking N atom) independently selected from O, S and N, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- group and wherein a sulphur atom in the ring may optionally be oxidised to an S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an 6-10 membered bicyclic saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further nitrogen atom (in addition to the linking N atom), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-; which ring is optionally substituted on an available carbon or nitrogen atom by 1 substituent selected from R^3;

R^8 is selected from $-OR^5$ and (1-4C)alkyl;

R^8 is selected from $-OR^5$ and (1-4C)alkyl;

HET-4 is a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S;

p is (independently at each occurrence) 0, 1 or 2;

m is 0 or 1;

n is 0, 1 or 2;

provided that when m is 0, then n is 1 or 2;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein:

R^1 is methyl;

R^2 is selected from $-C(O)NR^4R^5$, $-SO_2NR^4R^5$, $-S(O)_pR^4$ and HET-2;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 4-, 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2 or 3 heteroatoms independently selected from O, N and S, wherein a -CH2- group can optionally

be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring may optionally be oxidised to an S(O) or $S(O)_2$ group, which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano;

R^4 is selected from (1-4C)alkyl [substituted by 1 or 2 substituents independently selected from HET-2, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$];

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a 4-6 membered heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4;

R^7 is selected from -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to an S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8;

R^8 is selected from -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkylamino, di(1-4C)alkylamino, HET-3 (wherein said ring is unsubstituted), (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-4 is a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S;

p is (independently at each occurrence) 0, 1 or 2;

m is 0 or 1;

n is 0, 1 or 2;

provided that when m is 0, then n is 1 or 2;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein:

R^1 is methyl;

R^2 is selected from $-C(O)NR^4R^5$, $-SO_2NR^4R^5$, $-S(O)_pR^4$ and HET-2;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 4-, 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring may optionally be oxidised to an S(O) or $S(O)_2$ group, which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano;

R^4 is selected from (1-4C)alkyl [substituted by 1 or 2 substituents independently selected from HET-2, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$];

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a 4-6 membered heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4;

R^7 is selected from -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to an S(O) or

$S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an N-linked, 7 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further heteroatom (in addition to the linking N atom) independently selected from O, S and N, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- group and wherein a sulphur atom in the ring may optionally be oxidised to an S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an 6-10 membered bicyclic saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further nitrogen atom (in addition to the linking N atom), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-; which ring is optionally substituted on an available carbon or nitrogen atom by 1 substituent selected from R^3;

R^8 is selected from $-OR^5$ and (1-4C)alkyl;

R^8 is selected from -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkylamino, di(1-4C)alkylamino, HET-3 (wherein said ring is unsubstituted), (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-4 is a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S;

p is (independently at each occurrence) 0, 1 or 2;

m is 0 or 1;

n is 0, 1 or 2;

provided that when m is 0, then n is 1 or 2;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is a 5- or 6-membered heteroaryl ring;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl; R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

HET-2 is a 5- or 6- membered heterocyclyl ring as hereinbefore defined, containing 1 or 2 heteroatoms independently selected from O, N and S; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is a 5- or 6-membered heteroaryl ring;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is a 5- or 6- membered heterocyclyl ring as hereinbefore defined, containing 1 or 2 heteroatoms independently selected from O, N and S; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is selected from hydrogen, (1-4C)alkyl, [optionally substituted by $-OR^5$] and HET-2;

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from morpholino, furyl, imidazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, 2-pyrrolidonyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl and pyridazinyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is selected from hydrogen, (1-4C)alkyl, [optionally substituted by $-OR^5$] and HET-2;

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from morpholino, furyl, imidazolyl, isoxazolyl, oxadiazolyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, pyrrolidinyl, 2-pyrrolidonyl, tetrahydropyranyl, 1,1-dioxotetrahydrothienyl, and 2-oxoimidazolidinyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is selected from (1-4C)alkyl, [optionally substituted by $-OR^5$] and HET-2;

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from piperidinyl, piperazinyl, 3-oxopiperazinyl, 2-pyrrolidonyl, 2,5-dioxopyrrolidinyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 2-oxoimidazolidinyl, and 2,4-dioxoimidazolidinyl; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl oxadiazolyl;

R^3 is halo or trifluoromethyl;

R^4 is selected from (1-4C)alkyl, [optionally substituted by -OR^5] and HET-2;

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is piperidinyl or piperazinyl; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 ;

HET-1 is selected from thiazolyl, thiadiazolyl and pyrazolyl;

R^2 is –$CONR^4R^5$;

R^4 is piperidinyl optionally substituted with methyl;

$R^5$is hydrogen or methyl;

R^6 is methyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl and pyridazinyl;

R^2 is –$CONR^4R^5$ or –$SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is selected from (1-4C)alkyl, [optionally substituted by -OR^5] and HET-2;

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from piperidinyl, piperazinyl, 3-oxopiperazinyl, 2-pyrrolidonyl, 2,5-dioxopyrrolidinyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 2-oxoimidazolidinyl, and 2,4-dioxoimidazolidinyl; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl and pyridazinyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 is selected from (1-4C)alkyl, [optionally substituted by $-OR^5$] and HET-2;

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is piperidinyl or piperazinyl; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 and R^5 together with the nitrogen to which they are attached form a morpholino, piperidinyl, piperazinyl, pyrrolidinyl or azetidinyl ring, which ring is optionally substituted on a carbon or nitrogen atom by (1-4C)alkyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl and pyridazinyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 and R^5 together with the nitrogen to which they are attached form a morpholino, piperidinyl, piperazinyl, pyrrolidinyl or azetidinyl ring, which ring is optionally substituted on a carbon or nitrogen atom by (1-4C)alkyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 and R^5 together with the nitrogen to which they are attached form a morpholino, piperidinyl, piperazinyl, pyrrolidinyl or azetidinyl ring, which ring is optionally substituted on a carbon or nitrogen atom by R^8;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl; and

R^8 is selected from hydroxy, (1-4C)alkoxy and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^3 is halo or trifluoromethyl;

R^4 and R^5 together with the nitrogen to which they are attached form a morpholino, piperidinyl, piperazinyl, pyrrolidinyl or azetidinyl ring, which ring is optionally substituted on a carbon or nitrogen atom by R^8;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl; and

R^8 is pyrrolidine or piperidine;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0;

HET-1 is selected from thiazolyl, thiadiazolyl and pyrazolyl;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together with the nitrogen to which they are attached form a piperidinyl, or piperazinyl ring, which ring is optionally substituted on a carbon or nitrogen atom by (1-4C)alkyl or by a pyrrolidinyl ring;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0

HET-1 is selected from thiazolyl, thiadiazolyl and pyrazolyl;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together with the nitrogen to which they are attached form an azetidinyl ring which ring is optionally substituted on a carbon atom by hydroxy;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0;

HET-1 is selected from thiazolyl, thiadiazolyl and pyrazolyl;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together with the nitrogen to which they are attached form a 7-membered ring HET-3 which ring is optionally substituted on a carbon or nitrogen atom by methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0;

HET-1 is selected from thiazolyl, thiadiazolyl and pyrazolyl;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together with the nitrogen to which they are attached form a 6-10 membered bicyclic heterocyclic ring HET-3;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is a 5- or 6-membered heteroaryl ring;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

HET-2 is a 5- or 6- membered heterocyclyl ring as hereinbefore defined, containing 1 or 2 heteroatoms independently selected from O, N and S; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is a 5- or 6-membered heteroaryl ring;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is a 5- or 6- membered heterocyclyl ring as hereinbefore defined, containing 1 or 2 heteroatoms independently selected from O, N and S; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is selected from hydrogen, (1-4C)alkyl, [optionally substituted by $-OR^5$] and HET-2;

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl and $-C(O)NR^5R^5$];

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is selected from hydrogen, (1-4C)alkyl, [optionally substituted by $-OR^5$] and HET-2;

$R^5$is hydrogen or methyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0;

HET-1 is selected from thiazolyl, thiadiazolyl and pyrazolyl;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^4 is (1-4C)alkyl;

R^6 is methyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl;

R^2 is $-S(O)pR^4$;

p is 1 or 2;

R^3 is halo or trifluoromethyl;

R^4 is (1-4C)alkyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is a 5- or 6-membered heteroaryl ring;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^5 is hydrogen or (1-4C)alkyl;

HET-2 is a 5- or 6- membered heterocyclyl ring as hereinbefore defined, containing 1 or 2 heteroatoms independently selected from O, N and S; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^5 is hydrogen or methyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^5 is hydrogen or methyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^5 is hydrogen or methyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^5 is hydrogen or methyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; and

R^7 is selected from $-OR^5$ and (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from azetidinyl, morpholino, morpholinyl, piperidinyl, piperazinyl, 3-oxopiperazinyl, thiomorpholinyl, pyrrolidinyl, pyrrolidonyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2-oxazolidinonyl, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,1-dioxothiomorpholino, 1,3-dioxolanyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, pyranyl and 4-pyridonyl; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

In a further aspect of the invention is provided a compound of the formula (I) as hereinbefore defined wherein

R^1 is methyl;

m is 1 and n is 0 or 1;

HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl;

R^2 is HET-2;

R^3 is halo or trifluoromethyl;

R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl;

HET-2 is selected from furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, 1,2,4-triazolyl and 1,2,3-triazolyl; and

R^7 is (1-4C)alkyl;

or a salt, pro-drug or solvate thereof.

Further preferred compounds of the invention are each of the Examples, each of which provides a further independent aspect of the invention. In further aspects, the present invention also comprises any two or more compounds of the Examples.

In one aspect, particular compounds of the invention comprise any one or more of:

3-(1-methylethyl)oxy-5-{4-[(4-methylpiperazin-1-yl)carbonyl]phenoxy}-N-1,3-thiazol-2-ylbenzamide;

1-(4-{3-(1-methylethyl)oxy-5-[(1,3-thiazol-2-ylamino)carbonyl]phenoxy}benzoyl)prolinamide;

3-(4-{[[2-(dimethylamino)-2-oxoethyl](methyl)amino]carbonyl}phenoxy)-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-(1-methylethyl)oxy-5-{4-[(3-oxopiperazin-1-yl)carbonyl]phenoxy}-N-1,3-thiazol-2-ylbenzamide;

3-(4-{[(2-hydroxyethyl)(methyl)amino]carbonyl}phenoxy)-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-(4-{[(2-hydroxyethyl)amino]carbonyl}phenoxy)-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-(1-methylethyl)oxy-5-[4-({[2-(2-oxoimidazolidin-1-yl)ethyl]amino}carbonyl)phenoxy]-N-1,3-thiazol-2-ylbenzamide;

3-(4-{[(2-amino-2-oxoethyl)amino]carbonyl}phenoxy)-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-(1-methylethyl)oxy-5-[4-({[2-(methylamino)-2-oxoethyl]amino}carbonyl)phenoxy]-N-1,3-thiazol-2-ylbenzamide;

3-(1-methylethyl)oxy-5-(4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]carbonyl}phenoxy)-N-1,3-thiazol-2-ylbenzamide;

3-{4-[(4-hydroxypiperidin-1-yl)carbonyl]phenoxy}-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-(4-{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}phenoxy)-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-(1-methylethyl)oxy-5-(4-{[methyl(1-methylpiperidin-4-yl)amino]carbonyl}phenoxy)-N-1,3-thiazol-2-ylbenzamide;

3-[4-({[3-(1H-imidazol-1-yl)propyl]amino}carbonyl)phenoxy]-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-(1-methylethyl)oxy-5-{4-[(4-pyrrolidin-1-ylpiperidin-1-yl)carbonyl]phenoxy}-N-1,3-thiazol-2-ylbenzamide;

3-{4-[(dimethylamino)carbonyl]phenoxy}-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-(1-methylethyl)oxy-5-{4-[(methylamino)carbonyl]phenoxy}-N-1,3-thiazol-2-ylbenzamide;

3-(1-methylethyl)oxy-5-(4-{[(2-methoxyethyl)amino]carbonyl}phenoxy)-N-1,3-thiazol-2-ylbenzamide;

3-(4-{[(cyclopropylmethyl)amino]carbonyl}phenoxy)-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-(1-methylethyl)oxy-5-[4-({[2-(methylsulfonyl)ethyl]amino}carbonyl)phenoxy]-N-1,3-thiazol-2-ylbenzamide;

3-(1-methylethyl)oxy-5-[4-({[2-(2-oxopyrrolidin-1-yl)ethyl]amino}carbonyl)phenoxy]-N-1,3-thiazol-2-ylbenzamide;

3-[4-({[(1,1-dioxidotetrahydro-3-thienyl)methyl]amino}carbonyl)phenoxy]-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-{4-[(3-hydroxyazetidin-1-yl)carbonyl]phenoxy}-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-(1-methylethyl)oxy-5-[4-(morpholin-4-ylcarbonyl)phenoxy]-N-1,3-thiazol-2-ylbenzamide;

3-{4-[(4-acetylpiperazin-1-yl)carbonyl]phenoxy}-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-(1-methylethyl)oxy-5-(4-{[(1-methylpiperidin-4-yl)amino]carbonyl}phenoxy)-N-1,3-thiazol-2-ylbenzamide;

3-(4-{[(1H-imidazol-2-ylmethyl)amino]carbonyl}phenoxy)-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-[(1-methylethyl)oxy]-N-1,3-thiazol-2-ylbenzamide;

3-chloro-4-{3-(1-methylethyl)oxy-5-[(1,3-thiazol-2-ylamino)carbonyl]phenoxy}-N-(2-methoxyethyl)benzamide;

3-chloro-4-{3-(1-methylethyl)oxy-5-[(1,3-thiazol-2-ylamino)carbonyl]phenoxy}-N,N-dimethylbenzamide;

3-[4-(aminosulfonyl)-2-fluorophenoxy]-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-{2-chloro-4-[(dimethylamino)sulfonyl]phenoxy}-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-{2-chloro-4-[((1-methylethyl)amino)sulfonyl]phenoxy}-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-[2-chloro-4-(morpholin-4-ylsulfonyl)phenoxy]-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-{2-chloro-4-[(4-methylpiperazin-1-yl)sulfonyl]phenoxy}-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-[4-(aminosulfonyl)-5-chloro-2-fluorophenoxy]-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-[3-chloro-4-(morpholin-4-ylsulfonyl)phenoxy]-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-chloro-4-{3-(1-methylethyl)oxy-5-[(1,3-thiazol-2-ylamino)carbonyl]phenoxy}benzamide;

3-(1-methylethyl)oxy-5-[4-(methylsulfinyl)phenoxy]-N-1,3-thiazol-2-ylbenzamide;

3-{3-[(dimethylamino)carbonyl]phenoxy}-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-[4-(ethylthio)phenoxy]-5-(1-methylethyl)oxy-N-1,3-thiazol-2-ylbenzamide;

3-(1-methylethyl)oxy-5-[4-(1,3,4-oxadiazol-2-yl)phenoxy]-N-1,3-thiazol-2-ylbenzamide;

3-[4-(3,5-dimethylisoxazol-4-yl)phenoxy]-5-(1-methylethyl)oxy-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-[(4-furan-2-ylphenyl)oxy]-5-(1-methylethyl)oxy-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-[(4-furan-3-ylphenyl)oxy]-5-[(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-(1-methylethyl)oxy-N-(1-methyl-1H-pyrazol-3-yl)-5-[4-(methylsulfonyl)phenoxy]benzamide;

3-(1-methylethyl)oxy-5-[4-(methylsulfonyl)phenoxy]-N-1,3,4-thiadiazol-2-ylbenzamide;

3-(1-methylethyl)oxy-5-[4-(methylsulfonyl)phenoxy]-N-1,3-thiazol-2-ylbenzamide;

3-(1-methylethyl)oxy-5-[4-(methylsulfonyl)phenoxy]-N-pyridin-2-ylbenzamide;

3-(1-methylethyl)oxy-5-[4-(methylsulfonyl)phenoxy]-N-pyrazin-2-ylbenzamide;

3-(1-methylethyl)oxy-N-(5-methylisoxazol-3-yl)-5-[4-(methylsulfonyl)phenoxy]benzamide;
3-(1-methylethyl)oxy-N-isoxazol-3-yl-5-[4-(methylsulfonyl)phenoxy]benzamide;
N-[5-(2-furyl)-1,3,4-thiadiazol-2-yl]-3-(1-methylethyl)oxy-5-[4-(methylsulfonyl)phenoxy]benzamide; and
N-{4-[(dimethylamino)methyl]-1,3-thiazol-2-yl}-3-(1-methylethyl)oxy-5-[4-(methylsulfonyl)phenoxy]benzamide;
or a salt, pro-drug or solvate thereof.

The compounds of the invention may be administered in the form of a pro-drug. A pro-drug is a bioprecursor or pharmaceutically acceptable compound being degradable in the body to produce a compound of the invention (such as an ester or amide of a compound of the invention, particularly an in-vivo hydrolysable ester). Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen;

c) H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

f) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

The contents of the above cited documents are incorporated herein by reference.

Examples of pro-drugs are as follows. An in-vivo hydrolysable ester of a compound of the invention containing a carboxy or a hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include C_1 to C_6alkoxymethyl esters for example methoxymethyl, C_1 to C_6alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_3 to C_8cycloalkoxycarbonyloxyC_1 to C_6alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters.

A pharmaceutically-acceptable ester of a compound of the invention containing a hydroxy group includes inorganic esters such as phosphate esters and [illegible] α-acyloxyacyl

esters) and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a benzoxazinone derivative of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

A further feature of the invention is a pharmaceutical composition comprising a compound of Formula (I) as defined above, or a salt, solvate or prodrug thereof, together with a pharmaceutically-acceptable diluent or carrier.

According to another aspect of the invention there is provided a compound of Formula (I) as defined above for use as a medicament.

Further according to the invention there is provided a compound of Formula (I) for use in the preparation of a medicament for treatment of a disease mediated through GLK, in particular type 2 diabetes.

The compound is suitably formulated as a pharmaceutical composition for use in this way.

According to another aspect of the present invention there is provided a method of treating GLK mediated diseases, especially diabetes, by administering an effective amount of a compound of Formula (I) or salt, solvate or pro-drug thereof, to a mammal in need of such treatment.

Specific diseases which may be treated by a compound or composition of the invention include: blood glucose lowering in type 2 Diabetes Mellitus without a serious risk of hypoglycaemia (and potential to treat type 1), dyslipidemia, obesity, insulin resistance, metabolic syndrome X, impaired glucose tolerance.

As discussed above, thus the GLK/GLKRP system can be described as a potential "Diabesity" target (of benefit in both Diabetes and Obesity). Thus, according to another aspect of the invention there if provided the use of a compound of Formula (I) or salt, solvate or pro-drug thereof, in the preparation of a medicament for use in the combined treatment or prevention of diabetes and obesity.

According to another aspect of the invention there if provided the use of a compound of Formula (I) or salt, solvate or pro-drug thereof, in the preparation of a medicament for use in the treatment or prevention of obesity.

According to a further aspect of the invention there is provided a method for the combined treatment of obesity and diabetes by administering an effective amount of a compound of Formula (I) or salt, solvate or pro-drug thereof, to a mammal in need of such treatment.

According to a further aspect of the invention there is provided a method for the treatment of obesity by administering an effective amount of a compound of Formula (I) or salt, solvate or pro-drug thereof, to a mammal in need of such treatment.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium

carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the treated and the

particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula (I) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula (I) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

The elevation of GLK activity described herein may be applied as a sole therapy or in combination with one or more other substances and/or treatments for the indication being treated. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For example in the treatment of diabetes mellitus, chemotherapy may include the following main categories of treatment:

1) Insulin and insulin analogues;
2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide), prandial glucose regulators (for example repaglinide, nateglinide);
3) Agents that improve incretin action (for example dipeptidyl peptidase IV inhibitors, and GLP-1 agonists);
4) Insulin sensitising agents including PPARgamma agonists (for example pioglitazone and rosiglitazone), and agents with combined PPARalpha and gamma activity;

5) Agents that modulate hepatic glucose balance (for example metformin, fructose 1, 6 bisphosphatase inhibitors, glycogen phopsphorylase inhibitors, glycogen synthase kinase inhibitors);

6) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);

7) Agents that prevent the reabsorption of glucose by the kidney (SGLT inhibitors);

8) Agents designed to treat the complications of prolonged hyperglycaemia (for example aldose reductase inhibitors);

9) Anti-obesity agents (for example sibutramine and orlistat);

10) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (eg statins); PPARα agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); bile acid absorption inhibitors (IBATi) and nicotinic acid and analogues (niacin and slow release formulations);

11) Antihypertensive agents such as, β blockers (eg atenolol, inderal); ACE inhibitors (eg lisinopril); Calcium antagonists (eg. nifedipine); Angiotensin receptor antagonists (eg candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);

12) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors); antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin;

13) Agents which antagonise the actions of glucagon; and

14) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (eg. aspirin) and steroidal anti-inflammatory agents (eg. cortisone).

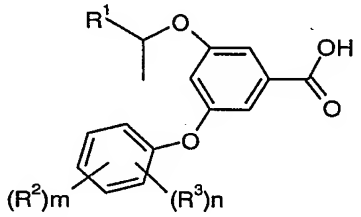
According to another aspect of the present invention there is provided individual compounds produced as end products in the Examples set out below and salts, solvates and pro-drugs thereof.

A compound of the invention, or a salt thereof, may be prepared by any process known to be applicable to the preparation of such compounds or structurally related compounds. Functional groups may be protected and deprotected using conventional methods. For examples of protecting groups such as amino and carboxylic acid protecting groups (as well as means of formation and eventual deprotection), see T. W. Greene and P. G. M. Wuts.

"Protective Groups in Organic Synthesis", Second Edition, John Wiley & Sons, New York, 1991.

Processes for the synthesis of compounds of Formula (I) are provided as a further feature of the invention. Thus, according to a further aspect of the invention there is provided a process for the preparation of a compound of Formula (I), which comprises a process a) to d) (wherein the variables are as defined hereinbefore for compounds of Formula (I) unless otherwise defined):

(a) reaction of an acid of Formula (III) or activated derivative thereof with a compound of Formula (IV),

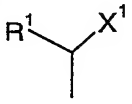


(III)

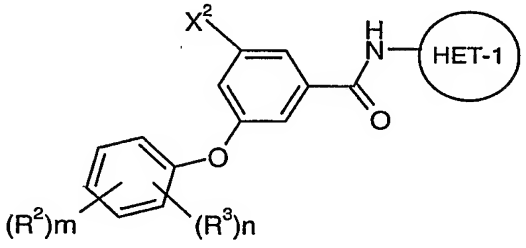
(IV);

or

(b) reaction of a compound of Formula (V) with a compound of Formula (VI),



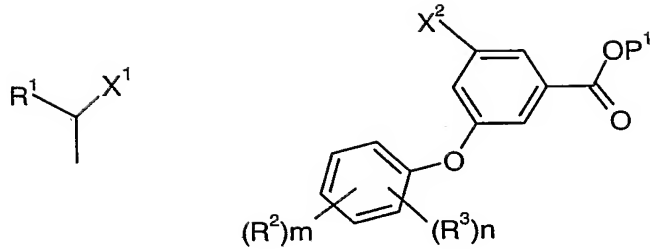
(V)



(VI)

wherein X^1 is a leaving group and X^2 is a hydroxyl group or X^1 is a hydroxyl group and X^2 is a leaving group;

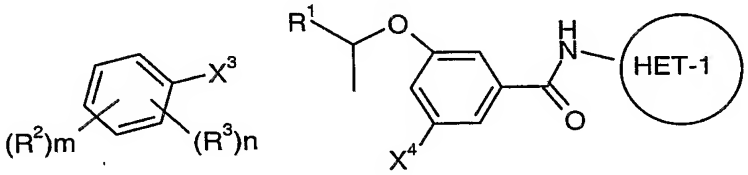
process (b) could also be accomplished using the intermediate ester Formula (VII), wherein P^1 is a protecting group as hereinafter described, followed by ester hydrolysis and amide formation by procedures described elsewhere and well known to those skilled in the art;



(VII)

or

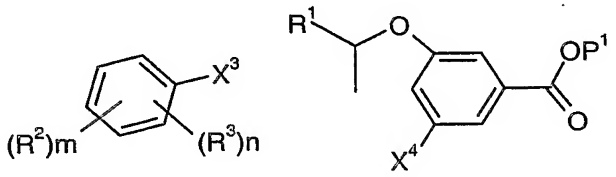
(c) reaction of a compound of Formula (VIII) with a compound of Formula (IX)



(VIII) (IX)

wherein X^3 is a leaving group or an organometallic reagent and X^4 is a hydroxyl group or X^3 is a hydroxyl group and X^4 is a leaving group or an organometallic reagent;

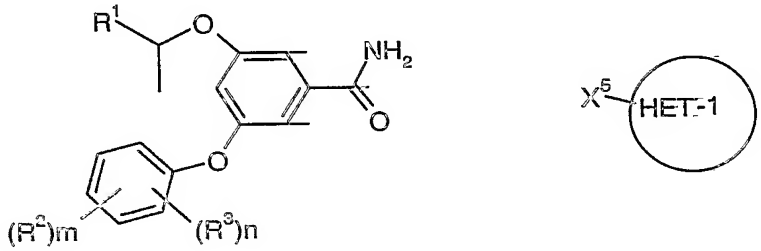
process (c) could also be accomplished using the intermediate ester Formula (X), followed by ester hydrolysis and amide formation by procedures described elsewhere and well known to those skilled in the art;



(X)

or

(d) reaction of a compound of Formula (XI) with a compound of Formula (XII),



(XI) (XII);

wherein X^5 is a leaving group;

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a salt, pro-drug or solvate thereof.

Suitable leaving groups X^1 to X^5 for processes b) to d) are any leaving group known in the art for these types of reactions, for example halo, alkoxy, trifluoromethanesulfonyloxy, methanesulfonyloxy, or p-toulenesulfonyloxy, or a group (such as a hydroxy group) that could be converted into a leaving group (such as an oxytriphenylphosphonium group) *in situ*.

Compounds of Formulae (III) to (XII) are commercially available, or are known in the art, or may be made by processes known in the art as shown in the accompanying Examples. For further information on processes for making such compounds, we refer to our PCT publications WO 03/000267, WO 03/015774 and WO 03/000262 and references therein.

Examples of conversions of a compound of Formula (I) into another compound of Formula (I), well known to those skilled in the art, include functional group interconversions such as hydrolysis,oxidation or reduction, and/or further functionalisation by standard reactions such as amide or metal-catalysed coupling, or nucleophilic displacement reactions;

Specific reaction conditions for the above reactions are as follows, wherein when P^1 is a protecting group P^1 is preferably C_{1-4}alkyl, for example methyl or ethyl:

Process a) – coupling reactions of amino groups with carboxylic acids to form an amide are well known in the art. For example,

(i) using an appropriate coupling reaction, such as a carbodiimide coupling reaction performed with EDAC in the presence of DMAP in a suitable solvent such as DCM, chloroform or DMF at room temperature; or

(ii) reaction in which the carboxylic group is activated to an acid chloride by reaction with oxalyl chloride in the presence of a suitable solvent such as methylene chloride. The acid chloride can then be reacted with a compound of Formula (IV) in the presence of a base, such as triethylamine or pyridine, in a suitable solvent such as chloroform or DCM at a temperature between 0°C and room temperature.

Process b) – compounds of Formula (V) and (VI) can be reacted together in a suitable solvent, such as DMF or THF, with a base such as sodium hydride or potassium *tert*-butoxide, at a temperature in the range 0 to 100°C, optionally using metal catalysis such as palladium(II)acetate, palladium on carbon, copper(II)acetate or copper(I)iodide; Alternatively, compounds of Formula (V) and (VI) can be reacted together in a suitable solvent, such as THF

or DCM, with a suitable phosphine such as triphenylphosphine, and azodicarboxylate such as diethylazodicarboxylate;

Process c) - compounds of Formula (VIII) and (IX) can be reacted together in a suitable solvent, such as DMF or THF, with a base such as sodium hydride or potassium tert-butoxide, at a temperature in the range 0 to 100°C, optionally using metal catalysis such as palladium(II)acetate, palladium on carbon, copper(II)acetate or copper(I)iodide;

Process d) – reaction of a compound of Formula (XI) with a compound of Formula (XII) can be performed in a polar solvent, such as DMF or a non-polar solvent such as THF with a strong base, such as sodium hydride or potassium *tert*-butoxide at a temperature between 0 and 100°C, optionally using metal catalysis, such as palladium(II)acetate, palladium on carbon, copper(II)acetate or copper(I)iodide.

Certain intermediates of formula (III), (VI), (VII), (IX) and/or (XI) are believed to be novel and comprise an independent aspect of the invention.

During the preparation process, it may be advantageous to use a protecting group for a functional group within the molecule. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (e.g. isopropyl, t-butyl); lower alkoxy lower alkyl groups (e.g. methoxymethyl, ethoxymethyl, isobutoxymethyl; lower aliphatic acyloxy lower alkyl groups, (e.g. acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (e.g. 1-methoxycarbonyloxyethyl, [illegible] lower alkyl groups [illegible]

p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (e.g. trimethylsilyl and t-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (e.g. trimethylsilylethyl); and (2-6C)alkenyl groups (e.g. allyl and vinylethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, metal- or enzymically-catalysed hydrolysis.

Examples of hydroxy protecting groups include lower alkenyl groups (e.g. allyl); lower alkanoyl groups (e.g. acetyl); lower alkoxycarbonyl groups (e.g. t-butoxycarbonyl); lower alkenyloxycarbonyl groups (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzoyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); tri lower alkyl/arylsilyl groups (e.g. trimethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl); aryl lower alkyl groups (e.g. benzyl) groups; and triaryl lower alkyl groups (e.g. triphenylmethyl).

Examples of amino protecting groups include formyl, aralkyl groups (e.g. benzyl and substituted benzyl, e.g. p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (e.g. t-butoxycarbonyl); lower alkenyloxycarbonyl (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl; trialkylsilyl (e.g. trimethylsilyl and t-butyldimethylsilyl); alkylidene (e.g. methylidene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base, metal- or enzymically-catalysed hydrolysis, or photolytically for groups such as o-nitrobenzyloxycarbonyl, or with fluoride ions for silyl groups.

Examples of protecting groups for amide groups include aralkoxymethyl (e.g. benzyloxymethyl and substituted benzyloxymethyl); alkoxymethyl (e.g. methoxymethyl and trimethylsilylethoxymethyl); tri alkyl/arylsilyl (e.g. trimethylsilyl, t-butyldimethylsily, t-butyldiphenylsilyl); tri alkyl/arylsilyloxymethyl (e.g. t-butyldimethylsilyloxymethyl, t-butyldiphenylsilyloxymethyl); 4-alkoxyphenyl (e.g. 4-methoxyphenyl); 2,4-di(alkoxy)phenyl (e.g. 2,4-dimethoxyphenyl); 4-alkoxybenzyl (e.g. 4-methoxybenzyl); 2,4-di(alkoxy)benzyl (e.g. 2,4-di(methoxy)benzyl); and alk-1-enyl (e.g. allyl, but-1-enyl and substituted vinyl e.g. 2-phenylvinyl).

Aralkoxymethyl, groups may be introduced onto the amide group by reacting the latter group with the appropriate aralkoxymethyl chloride, and removed by catalytic hydrogenation.

Alkoxymethyl, tri alkyl/arylsilyl and tri alkyl/silyloxymethyl groups may be introduced by reacting the amide with the appropriate chloride and removing with acid; or in the case of the silyl containing groups, fluoride ions. The alkoxyphenyl and alkoxybenzyl groups are conveniently introduced by arylation or alkylation with an appropriate halide and removed by oxidation with ceric ammonium nitrate. Finally alk-1-enyl groups may be introduced by reacting the amide with the appropriate aldehyde and removed with acid.

The following examples are for illustration purposes and are not intended to limit the scope of this application. Each exemplified compound represents a particular and independent aspect of the invention. In the following non-limiting Examples, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation in *vacuo* and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(iii) yields are given for illustration only and are not necessarily the maximum attainable;

(iv) the structures of the end-products of the Formula (I) were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis; and

(vi) Biotage cartridges refer to pre-packed silica cartridges (from 40g up to 400g), eluted using a biotage pump and fraction collector system; Biotage UK Ltd, Hertford, Herts, UK.

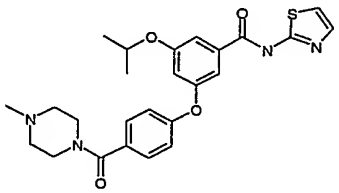
Abbreviations

DCM	dichloromethane;
DEAD	diethylazodicarboxylate;
DIAD	diisopropylazodicarboxylate;

DMSO	dimethyl sulphoxide;
DMF	dimethylformamide;
EDAC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride;
HPLC	high pressure liquid chromatography
HPMC	Hydroxypropylmethylcellulose;
LCMS	liquid chromatography / mass spectroscopy;
NMR	nuclear magnetic resonance spectroscopy
RT	room temperature; and
THF	tetrahydrofuran

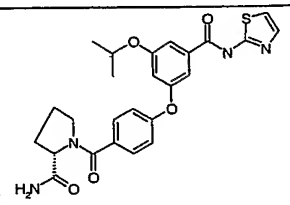
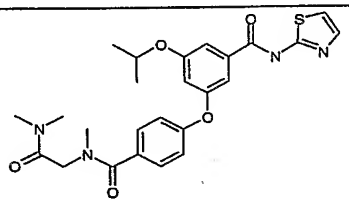
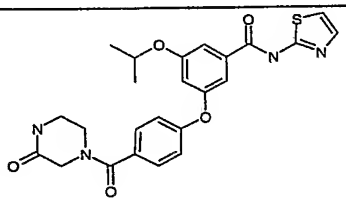
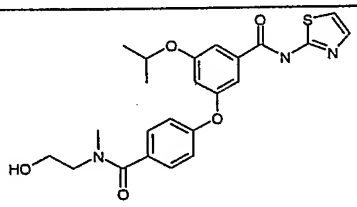
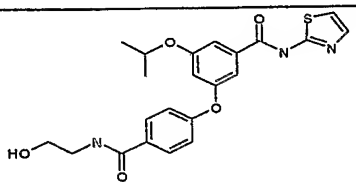
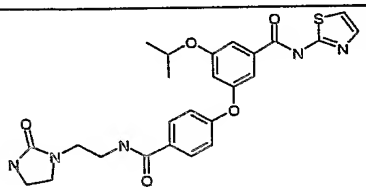
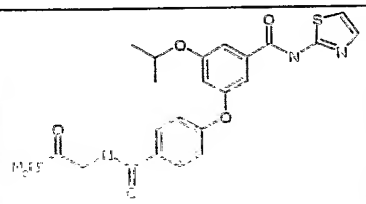
All compound names were derived using ACD NAME computer package.

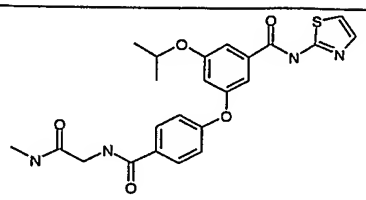
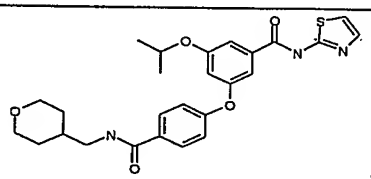
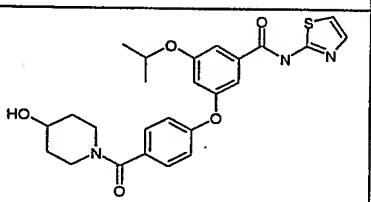
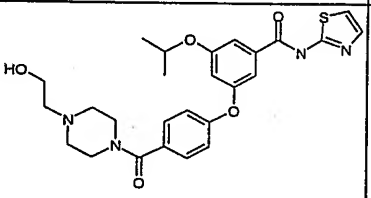
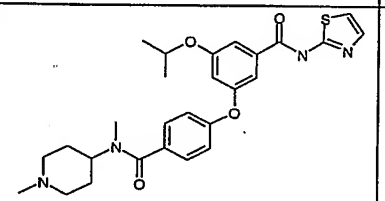
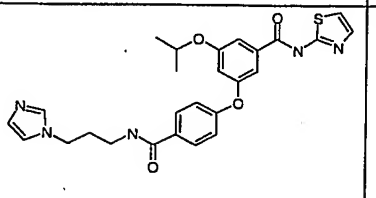
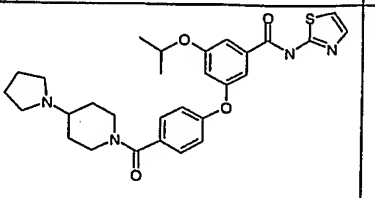
Example 1: 3-(1-Methylethyl)oxy-5-{4-[(4-methylpiperazin-1-yl)carbonyl]phenoxy}-N-1,3-thiazol-2-ylbenzamide

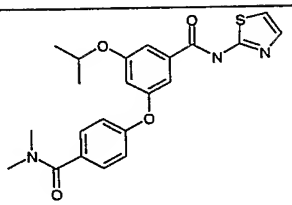
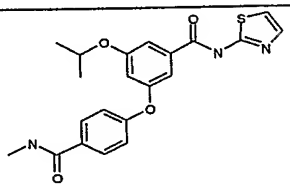
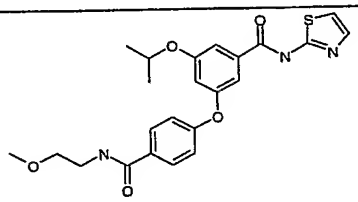
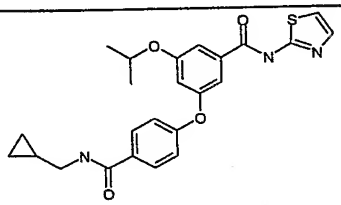
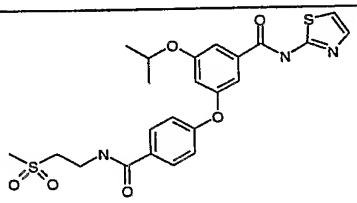
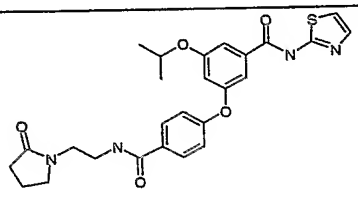
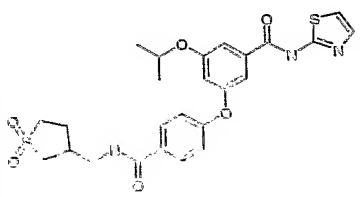


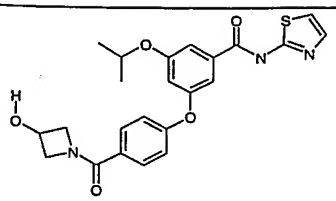
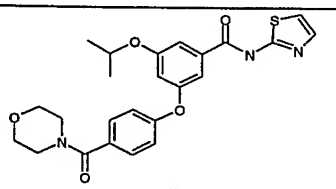
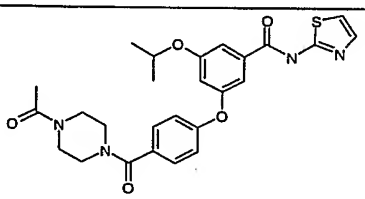
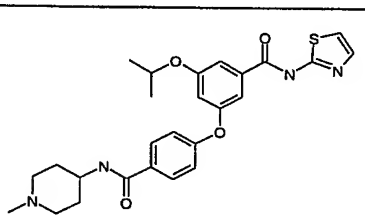
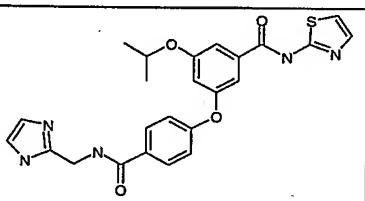
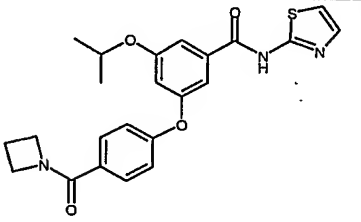
To a suspension of 4-({3-[(1-methylethyl)oxy]-5-[(1,3-thiazol-2-ylamino)carbonyl]phenyl} oxy)benzoic acid (100 mg), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (122 mg) and 1-methylpiperazine (32 mg) in DMF (2mL) was added diisopropylethylamine (0.11mL) and the mixture stirred at ambient temperature for 1 hour. Water (30mL) was added and the mixture extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica with 0-10% methanol in ethyl acetate as eluant to give the desired compound (103 mg). ^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 2.15 (s, 3H), 2.3 (s, 4H), 3.4-3.5 (br, 4H), 4.7-4.8 (m, 1H), 6.85 (s, 1H), 7.1 (d, 2H), 7.25 (d, 1H), 7.3 (s, 1H), 7.4 (d, 2H), 7.5 (s, 1H), 7.55 (d, 1H); *m/z* 481 $(M+H)^+$

In a similar manner, **Examples 1a-1aa** were also prepared:-

Example	Structure	*m/z*	NMR
1a		495 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.35 (d, 6H), 1.8-1.95 (br, 3H), 2.2-2.25 (br, 1H), 3.5-3.7 (br, 2H), 4.4 (br, 1H), 4.8 (m, 1H), 6.9 (s, 1H), 6.95 (s, 1H), 7.1-7.2 (d, 2H), 7.35 (d, 1H), 7.4 (s, 1H), 7.55 (s, 1H), 7.6 (d, 1H), 7.7 (d, 1H), 12.63 (s, 1H)
1b		497 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 2.65-3.0 (m, 9H), 4.1-4.3 (br, 2H), 4.7-4.8 (m, 1H), 6.8 (s, 1H), 7.1-7.2 (d, 2H), 7.25 (d, 1H), 7.3 (m, 1H), 7.4-7.55 (m, 2H), 7.7 (d, 1H), 7.95 (s, 1H), 12.6 (s, 1H)
1c		481 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 3.25 (m, 2H), 3.6-3.7 (br, 2H), 4.0 (m, 2H), 4.7-4.8 (m, 1H), 6.85 (s, 1H), 7.1 (d, 2H), 7.25 (d, 1H), 7.3 (s, 1H), 7.45-7.55 (m, 4H), 8.05 (s, 1H), 12.6 (s, 1H)
1d		456 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 2.95 (s, 3H), 3.4-3.6 (br, 4H), 4.7 (t, 1H), 4.7-4.8 (m, 1H), 6.8 (s, 1H), 7.1 (d, 2H), 7.25 (d, 1H), 7.3 (s, 1H), 7.4-7.5 (m, 3H), 7.55 (d, 1H), 12.6 (s, 1H)
1e		442 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 3.35 (m, 2H), 3.5 (m, 2H), 4.7 (t, 1H), 4.7-4.8 (m, 1H), 6.8 (s, 1H), 7.1 (d, 2H), 7.25 (d, 2H), 7.3 (s, 1H), 7.35 (d, 1H), 7.9 (d, 2H), 8.4 (t, 1H), 12.6 (s, 1H)
1f		510 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 3.2 (m, 4H), 3.4 (m, 4H), 4.75 (m, 1H), 6.25 (s, 1H), 6.85 (s, 1H), 7.1 (d, 2H), 7.25 (d, 2H), 7.5 (s, 1H), 7.55 (d, 1H), 7.85 (d, 2H), 8.45 (t, 1H), 12.6 (s, 1H)
1g		455 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 3.85 (d, 2H), 4.7-4.8 (m, 1H), 6.9 (s, 1H), 7.05 (s, 1H), 7.2 (d, 2H), 7.35 (d, 2H), 7.4 (s, 1H), 7.55 (s, 1H), 7.6 (d, 1H), 8.0 (d, 2H), 8.65 (t, 1H), 12.7 (s, 1H)

1h		469 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 2.6 (d, 3H), 3.85 (d, 2H), 4.7-4.8 (m, 1H), 6.85 (s, 1H), 7.1 (d, 1H), 7.25 (d, 2H), 7.3 (s, 1H), 7.35 (d, 2H), 7.7-7.8 (br, 1H), 7.95 (d, 2H), 8.65 (t, 1H), 12.7 (s, 1H)
1i		496 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.15-1.2 (m, 2H), 1.3 (d, 6H), 1.55-1.6 (d, 2H), 1.5-1.6 (m, 1H), 3.15 (t, 2H), 3.35 (t, 2H), 3.8 (d, 2H), 4.75 (m, 1H), 6.8 (s, 1H), 7.1 (d, 2H), 7.25 (d, 2H), 7.45 (s, 1H), 7.5 (d, 1H), 7.9 (d, 2H), 8.45 (t, 1H), 12.6 (s, 1H)
1j		482 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 1.35 (br, 2H), 1.7-1.8 (br, 2H), 2.65 (s, 6H), 3.15 (t, 2H), 3.7 (m, 2H), 4.7 (t, 1H), 4.7-4.8 (m, 1H), 6.8 (s, 1H), 7.1 (d, 2H), 7.25 (d, 1H), 7.3 (s, 1H), 7.4 (d, 1H), 7.5 (s, 1H), 7.55 (d, 1H), 12.6 (s, 1H)
1k		511 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 2.4 (m, 6H), 3.5 (m, 6H), 4.4 (t, 1H), 4.7-4.8 (m, 1H), 6.8 (s, 1H), 7.1 (d, 2H), 7.25 (d, 1H), 7.3 (s, 1H), 7.4 (d, 2H), 7.5 (s, 1H), 7.55 (d, 1H), 12.6 (s, 1H)
1l		509 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 1.5-1.6 (br, 2H), 1.65-1.8 (br, 2H), 2.05 (s, 3H), 2.75 (br, 1H), 2.8 (s, 3H), 3.3 (br, 4H), 4.7-4.8 (m, 1H), 6.7 (s, 1H), 7.0 (d, 1H), 7.05 (d, 2H), 7.3 (s, 1H), 7.4 (m, 3H), 7.5 (s, 1H), 12.6 (s, 1H)
1m		506 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 2.0 (dt, 2H), 3.3 (t, 2H), 4.1 (t, 2H), 4.8 (m, 1H), 6.9 (s, 1H), 6.95 (s, 1H), 7.2 (d, 2H), 7.25 (s, 1H), 7.3 (d, 2H), 7.55 (s, 1H), 7.6 (d, 1H) 7.7 (s, 1H), 7.95 (d, 2H), 8.55 (t, 1H), 12.6 (s, 1H)
1n		535 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 1.65 (s, 4H), 1.8 (br, 2H), 2.2 (br, 1H), 3.0 (br, 1H), 3.3 (s, 9H), 4.7-4.8 (m, 1H), 6.7 (s, 1H), 6.9 (s, 1H), 7.05 (d, 2H), 7.3 (s, 1H), 7.35 (d, 1H), 7.4 (d, 2H), 7.5 (s, 1H), 12.6 (s, 1H)

1o[$]		426 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 2.95 (s, 6H), 4.7-4.8 (m, 1H), 6.8 (s, 1H), 7.1 (d, 2H), 7.25 (d, 1H), 7.3 (d, 1H), 7.4-7.55 (m, 4H), 12.7 (s, 1H)
1p[$]		412 $(M+H)^+$	
1q[$]		456 $(M+H)^+$	
1r[$]		452 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 0.7-1.15 (m, 5H), 1.2 (d, 6H), 3.0 (t, 2H), 4.8 (m, 1H), 6.7 (s, 1H), 7.0 (d, 2H), 7.15 (d, 2H), 7.35 (s, 1H), 7.4 (d, 1H) 7.8 (d, 2H), 8.4 (t, 1H), 12.7 (s, 1H)
1s[$]		502 $(M+H)^+$	
1t[$]		507 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 1.8-1.9 (dt, 2H), 2.1-2.2 (t, 2H), 3.3-3.4 (m, 6H), 4.7-4.8 (m, 1H), 6.8 (s, 1H), 7.1 (d, 2H), 7.25 (m, 2H), 7.5 (s, 1H), 7.5 (d, 1H) 7.85 (d, 2H), 8.45 (t, 1H), 12.6 (s, 1H)
1u[$]		528 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 1.8-1.9 (m, 1H), 2.2 (m, 1H), 2.6 (m, 1H), 2.85 (m, 1H), 3.0 (m, 1H), 3.1-3.2 (m, 2H), 3.4 (t, 2H), 4.7-4.8 (m, 1H), 6.8 (s, 1H), 7.1 (d, 2H), 7.25 (d, 2H), 7.5 (s, 1H), 7.55 (d, 1H) 7.9 (d, 2H), 8.6 (t, 1H), 12.7 (s, 1H)

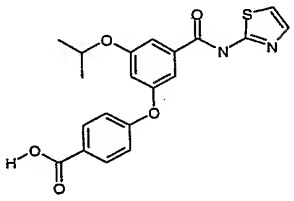
1v[$]		454 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 3.7-4.5 (br, 5H), 4.7-4.8 (m, 1H), 5.7 (d, 1H), 6.8 (s, 1H), 7.05 (d, 2H), 7.25 (d, 1H), 7.3 (d, 1H), 7.5 (s, 1H), 7.55 (d, 1H) 7.65 (d, 2H), 12.7 (s, 1H)
1w[$]		466 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 3.5 (br, 4H), 3.6 (br, 4H), 4.7-4.8 (m, 1H), 6.8 (s, 1H), 7.1 (d, 2H), 7.25 (d, 1H), 7.3 (d, 1H), 7.4-7.55 (m, 4H), 12.6 (s, 1H)
1x[$]		509 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 2.0 (s, 3H), 3.4-3.6 (br, 8H), 4.7-4.8 (m, 1H), 6.8 (s, 1H), 7.1 (d, 2H), 7.25 (d, 1H), 7.3 (d, 1H), 7.4-7.55 (m, 4H), 12.7 (s, 1H)
1y[$]		495 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 1.5-1.6 (m, 2H), 1.7-1.8 (m, 2H), 1.9-2.0 (m, 2H), 2.1 (s, 3H), 2.7-2.8 (d, 2H), 3.6-3.75 (br, 1H), 4.7-4.8 (m, 1H), 6.7 (s, 1H), 7.05 (d, 1H), 7.1 (d, 2H), 7.25 (s, 1H), 7.4 (d, 1H), 7.5 (s, 1H) 7.87 (d, 2H), 8.2 (d, 1H), 12.7 (s, 1H)
1z[$]		478 $(M+H)^+$	
1aa*		438 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.35 (d, 6H), 2.36 (m, 2H), 4.20-4.38 (m, 4H), 4.58 (m, 1H), 6.78 (m, 1H), 7.00 (m, 3H), 7.17 (m, 1H), 7.27 (m, 2H), 7.63 (d, 2H)

[$]1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride used as coupling reagent in place of *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.

*Ethyl acetate was used as eluant.

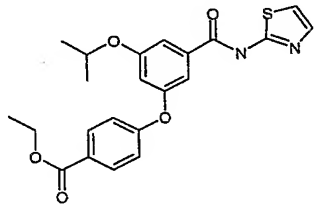
The required acid for Example 1 was prepared as described below:

4-({3-[(1-Methylethyl)oxy]-5-[(1,3-thiazol-2-ylamino)carbonyl]phenyl}oxy)benzoic acid



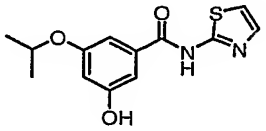
A solution of ethyl 4-({3-[(1-methylethyl)oxy]-5-[(1,3-thiazol-2-ylamino)carbonyl]phenyl} oxy)benzoate (2.5g) in THF (100 mL) was added to a solution of lithium hydroxide monohydrate (1.3g) in water (50mL). The mixture was stirred at ambient temperature for 16 hours and the THF removed *in vacuo*. The aqueous layer was acidified with 1M hydrochloric acid (30mL), the solid precipitate filtered off, washed with water and dried *in vacuo* to give the desired compound (2.22g). ^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 4.7-4.8 (m, 1H), 6.9 (t, 1H), 7.1 (d, 2H), 7.25 (d, 1H), 7.35 (s, 1H), 7.5 (s, 1H), 7.55 (d, 1H), 7.95 (d, 2H), 12.75 (s, 1H); *m/z* 399 $(M+H)^+$

Ethyl 4-({3-[(1-methylethyl)oxy]-5-[(1,3-thiazol-2-ylamino)carbonyl]phenyl}oxy) benzoate



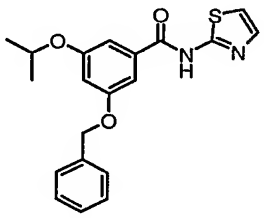
A solution of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide (3.06g), 4-ethoxycarbonylphenylboronic acid (3.0g), copper (II) acetate (3.0g), triethylamine (7.6mL) and freshly activated 4Å molecular sieves (12g) in dichloromethane (170mL) was stirred at ambient temperature and under ambient atmosphere for 2 days. The reaction mixture was filtered through diatomaceous earth, washed with dichloromethane (2 x 50mL), the dichloromethane removed *in vacuo* and the residual oil partitioned between ethyl acetate (150mL) and 1M hydrochloric acid (100mL). The ethyl acetate layer was separated, washed with aqueous sodium hydrogen carbonate solution and brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica with 20% ethyl acetate in isohexane as eluant to give the desired compound (2.64g). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 6H), 1.35 (t, 3H), 4.35 (q, 2H), 4.5-4.6 (m, 1H), 6.8 (s, 1H), 6.95 (s, 1H), 7.0 (d, 2H), 7.15 (s, 1H), 7.2 (s, 1H), 7.3 (d, 1H), 8.05 (d, 2H); *m/z* 427 $(M+H)^+$

3-Hydroxy-5-[(1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide



3-[(1-Methylethyl)oxy]-5-[(phenylmethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide (11.17g) was dissolved in trifluoroacetic acid (60mL) and treated with thioanisole (17.8mL). The mixture was left to stir at ambient temperature for 18 hours before the trifluoroacetic acid was removed *in vacuo*. The residues were treated with isohexane (100 mL) and the solid filtered off, before being washed with further isohexane (2 x 20 mL). The solid was dissolved in ethyl acetate (200 mL) and washed with aqueous saturated sodium hydrogen carbonate solution (100 mL). The organics were washed with water (100 mL) and brine (100 mL), and dried ($MgSO_4$) before evaporation *in vacuo* to afford a solid which was washed with isohexane (200 mL) and dried *in vacuo* to give the desired compound (7.18g). ^{1}H NMR δ (d_6-DMSO): 1.27 (d, 6H), 4.55 (m, 1H), 6.49 (m, 1H), 7.02 (s, 1H), 7.14 (s, 1H), 7.25 (d, 1H), 7.54 (d, 1H), 9.73 (s, 1H), 12.44 (s, 1H); m/z 279 $(M+H)^+$, 277 $(M-H)^-$

3-[(1-Methylethyl)oxy]-5-[(phenylmethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide



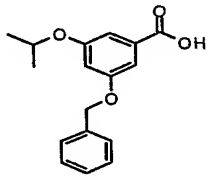
To a solution of 3-[(1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoic acid (20g) in dichloromethane (400 mL), cooled to 0°C was slowly added oxalyl chloride (12.18 mL) and DMF (0.4 mL), with stirring. The mixture was allowed to warm to ambient temperature and stirred for a further 16 hours, following which the organics were removed *in vacuo*, and the residues azeotroped with toluene (100mL). The crude material was dissolved in dichloromethane (200 mL) and slowly added to a stirred suspension of 2-aminothiazole (10.48g) and diisopropylethylamine (24.3 mL), in dichloromethane (200 mL). The mixture was stirred at ambient temperature for 70 hours, before the organics were removed *in vacuo*. The residues were dissolved in ethyl acetate (300 mL) and washed with 1M aqueous hydrochloric acid (300 mL). The aqueous layer was extracted with further ethyl acetate (300 mL), and the combined organics washed with brine (75 mL), and dried ($MgSO_4$), before

evaporation *in vacuo* to give the desired compound (28.02g) which was used without further purification.

^{1}H NMR δ (d_6-DMSO): 1.27 (d, 6H), 4.70 (m, 1H), 5.15 (s, 2H), 6.77 (m, 1H), 7.27 (m, 2H), 7.33-7.47 (brm, 6H), 7.55 (d, 1H); m/z 369 $(M+H)^+$, 367 $(M-H)^-$;

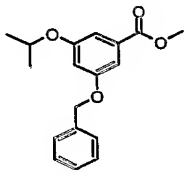
The ^{1}H NMR spectrum also contained signals consistent with a small amount of ethyl acetate.

3-[(1-Methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoic acid



To a solution of methyl 3-[(1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoate (37g) in a 1:1 mixture of THF:methanol (300 mL) was added 4M sodium hydroxide solution (150mL). The mixture was refluxed for 45 minutes, following which the organics were removed *in vacuo*. The aqueous was acidified to pH4 with hydrochloric acid (2M), and extracted with ethyl acetate. The organics were combined, washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the desired compound (33.45g), which was used without further purification. ^{1}H NMR δ (d_6-DMSO): 1.26 (d, 6H), 4.59-4.69 (m, 1H), 5.15 (s, 2H), 6.80 (app t, 1H), 7.04 (m, 1H), 7.12 (m, 1H), 7.33 (app t, 1H), 7.40 (t, 2H), 7.46 (d, 2H), 12.95 (s, 1H)

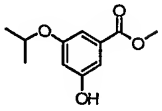
Methyl 3-[(1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoate



To a solution of methyl 3-hydroxy-5-[(1-methylethyl)oxy]benzoate (25g) in DMF (250 mL) was added anhydrous potassium carbonate (297 mmol), and benzyl bromide (143 mmol). The mixture was stirred at 60°C for 5 hours, then cooled to room temperature. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organics were combined and washed with further water, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the desired compound (37g) which was used without further purification.

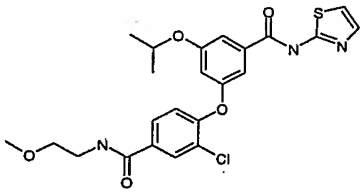
^{1}H NMR δ (d_6-DMSO): 1.26 (d, 6H), 3.84 (s, 3H), 4.61-4.70 (m, 1H), 5.12 (s, 2H), 6.84 (t, 1H), 7.32 (app t, 1H), 7.12 (m, 1H), 7.31-7.37 (m, 1H), 7.40 (t, 2H), 7.46 (d, 2H),

Methyl 3-hydroxy-5-[(1-methylethyl)oxy]benzoate



To a stirred solution of methyl 3,5-dihydroxybenzoate (0.1 mol) in DMF (180 mL) was added powdered potassium carbonate (0.2 mol) and 2-iodopropane (0.1 mol), and the resulting mixture stirred at ambient temperature for 16 hours. The reaction mixture was poured into water (1000 mL) and the mixture extracted with ether. The extracts were combined and washed sequentially with water (twice) and brine; the solution was dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the crude product as a pale yellow oil (12.6g). This was treated with toluene (40 mL) and allowed to stand overnight. The insoluble material (starting phenol) was removed by filtration, and the filtrate evaporated *in vacuo*. The resulting oil was chromatographed (2 x 90 g Biotage silica cartridges), eluting with hexane containing ethyl acetate (10% increasing to 15% v/v). The title compound was obtained as an oil (25% yield), which was identical by tlc to a sample prepared by a similar procedure. ^{1}H NMR δ (d_6-DMSO): 1.2 (d, 6H), 3.8 (s, 3H), 4.5 – 4.6 (hept, 1H), 6.55 (m, 1H), 7.85 (m, 1H), 7.95 (m, 1H), 9.8 (s, 1H)

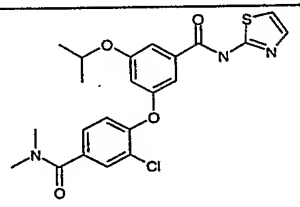
Example 2: 3-Chloro-4-{3-(1-methylethyl)oxy-5-[(1,3-thiazol-2-ylamino)carbonyl] phenoxy}-N-(2-methoxyethyl)benzamide



To a suspension of 3-chloro-4-({3-[(1-methylethyl)oxy]-5-[(1,3-thiazol-2-ylamino)carbonyl] phenyl}oxy)benzoic acid (107 mg), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (122 mg) and 2-methoxyethylamine (38 mg) in DMF (2mL) was added diisopropylethylamine (0.11mL) and the mixture stirred at ambient temperature for 1 hour. Water (30mL) was added and the mixture extracted with ethyl acetate (3 x 15mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica with ethyl acetate as eluant to give the desired compound (85 mg). ^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 3.25 (s, 3H), 3.4 (m, 4H), 4.7-4.8 (m,

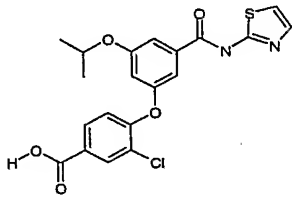
1H), 6.85 (d, 1H), 7.2 (m, 1H), 7.5 (s, 1H), 7.55 (d, 1H), 7.8 (m, 1H), 8.05 (dd, 1H), 8.6 (t, 1H); *m/z* 486 $(M+H)^+$.

In a similar manner, **Example 2a** was also prepared:-

Example	Structure	*m/z*	NMR
2a		460 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 2.95 (s, 6H), 4.7-4.8 (m, 1H), 6.8 (s, 1H), 7.2 (m, 2H), 7.25 (d, 1H), 7.4 (dd, 1H), 7.5 (s, 1H), 7.55 (d, 1H), 7.65 (s, 1H), 12.6 (s, 1H)

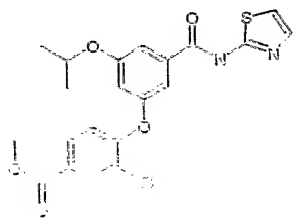
The required acid for Example 2 was prepared as described below:-

3-Chloro-4-({3-[(1-methylethyl)oxyl-5-[(1,3-thiazol-2-ylamino)carbonyl]phenyl} oxy)benzoic acid



A solution of methyl 3-chloro-4-({3-[(1-methylethyl)oxy]-5-[(1,3-thiazol-2-ylamino) carbonyl]phenyl}oxy)benzoate (950mg) in THF (30 mL) was added to a solution of lithium hydroxide monohydrate (237mg) in water (15mL). The mixture was stirred at ambient temperature for 16 hours and the THF removed *in vacuo*. The aqueous layer was acidified with 1M hydrochloric acid (5.3mL), the solid precipitate filtered off, washed with water and dried *in vacuo* to give the desired acid (880mg). ^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 4.7-4.8 (m, 1H), 6.9 (t, 1H), 7.15 (d, 1H), 7.25 (d, 2H), 7.5 (d, 1H), 7.55 (s, 1H), 7.9 (d, 1H), 8.05 (d, 1H), 12.75 (s, 1H)

Methyl 3-chloro-4-({3-[(1-methylethyl)oxyl-5-[(1,3-thiazol-2-ylamino)carbonyl]phenyl} oxy)benzoate



To a solution of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide (208mg) and methyl 3-chloro-4-fluorobenzoate (141mg) in acetonitrile (5mL) was added potassium carbonate (104mg) and the stirred mixture heated at 160°C in a 'Smith Creator Microwave' for 30 minutes. The mixture allowed to return to ambient temperature and pressure, the acetonitrile evaporated, and the residue partitioned between ethyl acetate (50mL) and water (20mL). The organic layer was separated, washed with brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica (eluting with 30% ethyl acetate in isohexane) to give the desired ester (178mg). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 6H), 3.9 (s, 3H), 4.5-4.6 (m, 1H), 6.75 (t, 1H), 6.95 (d, 1H), 7.0 (d, 1H), 7.1 (s, 1H), 7.2 (m, 1H), 7.3 (s, 1H), 7.9 (dd, 1H), 8.05 (d, 1H); *m/z* 447 $(M+H)^+$

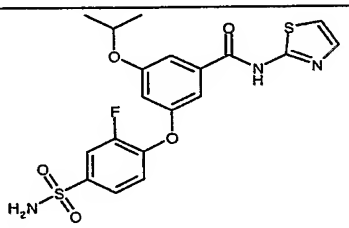
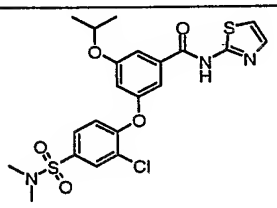
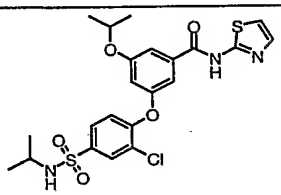
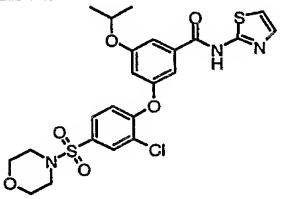
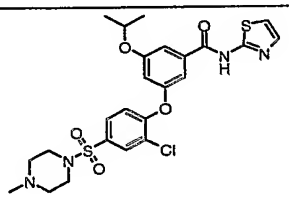
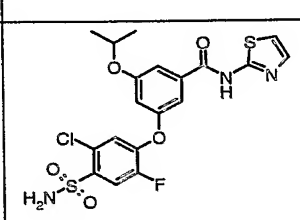
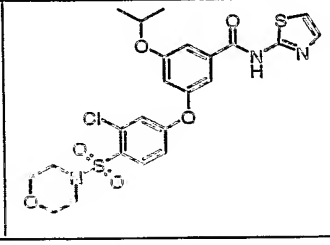
The synthesis of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide is described above in Example 1.

Example 3: General Procedure for Preparation of Halogenated Sulphonamides

To a solution of the appropriate amine (1.8 mmol) in dichloromethane (2 mL), was added the sulphonyl chloride (0.72 mmol) in dichloromethane (2 mL), and the resulting mixture stirred for 18 hours. The mixture was treated with 1M aqueous hydrochloric acid (4 mL) and the organics separated. Evaporation *in vacuo* gave the crude fluorosulphonamide which was used without further purification.

To a solution of the crude fluorosulphonamide (7.2 mmol) in acetonitrile (3 mL), was added 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide (0.36 mmol) and potassium carbonate (1.8 mmol). The mixture was heated to 170°C in a 'Smith Creator Microwave' for 100 minutes, before being filtered and the resultant organics evaporated *in vacuo*. The residues were then chromatographed on a Redisep (12g, SiO_2) cartridge using an Isco Optix chromatography system, eluting with 30 to 100% ethyl acetate in isohexane, and evaporated *in vacuo* to afford the desired compound.

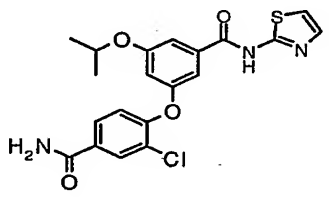
Using a similar procedure to that described above, **Examples 3a-3g** were prepared from 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide:-

Example	Structure	*m/z*	NMR
3a		452 $(M+H)^+$ 450 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.28 (d, 6H), 4.70-4.80 (m, 1H), 6.93 (m, 1H), 7.26 (m, 2H), 7.37 (t, 1H), 7.47 (s, 2H), 7.54 (m, 2H), 7.68 (d, 1H), 7.80 (dd, 1H), 12.64 (s, 1H)
3b		496, 498 $(M+H)^+$ 494, 496 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.30 (d, 6H), 2.64 (s, 6H), 4.72-4.82 (m, 1H), 6.97 (m, 1H), 7.20-7.28 (m, 2H), 7.36 (m, 1H), 7.53 (m, 2H), 7.70 (dd, 1H), 7.92 (d, 1H), 12.64 (s, 1H)
3c		510, 512 $(M+H)^+$ 508, 510 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 0.98 (d, 6H), 1.30 (d, 6H), 4.68-4.79 (m, 2H), 6.92 (s, 1H), 7.21-7.31 (m, 3H), 7.53 (m, 2H), 7.66 (d, 2H), 7.76 (dd, 1H), 7.97 (m, 1H), amide NH not seen
3d		538, 540 $(M+H)^+$ 536, 538 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.29 (d, 6H), 2.93 (m, 4H), 3.64 (m, 4H), 4.73-4.83 (m, 1H), 6.98 (m, 1H), 7.26 (m, 2H), 7.37 (s, 1H), 7.54 (m, 2H), 7.69 (dd, 1H), 7.91 (m, 1H), 12.63 (s, 1H)
3e[$]		551, 553 $(M+H)^+$ 549, 551 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.30 (d, 6H), 2.13 (m, 3H), 2.34 (s, 4H), 2.93 (s, 4H), 4.72-4.81 (m, 1H), 6.96 (s, 1H), 7.20-7.30 (m, 2H), 7.36 (s, 1H), 7.54 (s, 1H), 7.65-7.78 (m, 2H), 7.90 (m, 1H), amide NH not seen
3f		486, 488 $(M+H)^+$ 484, 486 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.29 (d, 6H), 4.70-4.82 (m, 1H), 6.97 (s, 1H), 7.26 (m, 2H), 7.30 (s, 1H), 7.47 (d, 1H), 7.54 (m, 2H), 7.73 (s, 1H), 7.92 (d, 1H), amide NH not seen
3g		538, 540 $(M+H)^+$ 536, 538 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.30 (d, 6H), 3.12 (m, 4H), 3.61 (m, 4H), 4.70-4.80 (m, 1H), 7.02 (m, 1H), 7.12 (dd, 1H), 7.28 (d, 1H), 7.36 (d, 1H), 7.44 (m, 1H), 7.57 (m, 2H), 7.95 (d, 1H), 12.64 (s, 1H)

[$] The requisite sulfonamide for this example was prepared using a 1:1 ratio of amine : sulfonyl chloride, and isolated by treatment with 0.1 aqueous sodium hydroxide.

The synthesis of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide is described in Example 1 above.

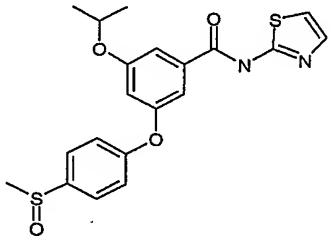
Example 4 : 3-Chloro-4-{3-(1-methylethyl)oxy-5-[(1,3-thiazol-2-ylamino)carbonyl] phenoxy}benzamide



To a solution of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide (105 mg) and 3-chloro-4-fluorobenzamide (87 mg) in acetonitrile (3 mL) was added potassium carbonate (138 mg) and the stirred mixture heated at 150^0 in a 'Smith Creator Microwave' for 1 hour. The mixture was allowed to return to ambient temperature and pressure, the acetonitrile evaporated, the residue partitioned between water (20 mL) and ethyl acetate (50 mL), the organic layer separated, washed with brine, dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica with ethyl acetate as eluant to give the desired compound (42 mg). ^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 4.7-4.8 (m, 1H), 6.8 (s, 1H), 7.2 (d, 2H), 7.25 (d, 1H), 7.5 (s, 2H), 7.55 (d, 1H), 7.85 (dd, 1H), 8.05 (m, 1H), 12.6 (s, 1H); *m/z* 432 $(M+H)^+$

The synthesis of 3-hydroxy-5-[(1-methylethyl)oxy]-N-1,3-thiazol-2-ylbenzamide is described in Example 1 above.

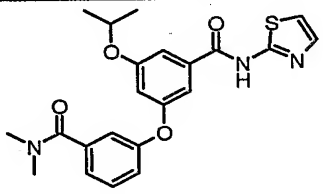
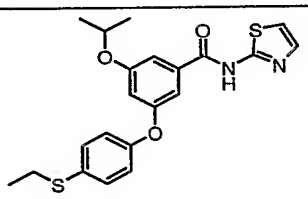
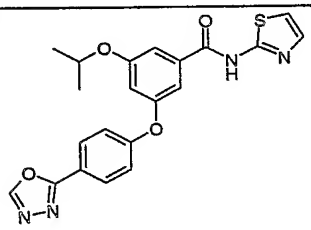
Example 5: 3-(1-methylethyl)oxy-5-[4-(1,3,4-oxadiazol-2-yl)phenoxy]-N-1,3-thiazol-2-ylbenzamide



A solution of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide (280 mg), 4-(methanesulphinyl)benzeneboronic acid (368 mg), copper (II) acetate (363 mg), triethylamine (0.700mL) and freshly activated 4Å molecular sieves (1.4g) in dichloromethane (10mL), was stirred at ambient temperature and under ambient atmosphere for 3 days. The reaction

mixture was filtered through diatomaceous earth, washed with dichloromethane (2 x 10mL), the dichloromethane removed *in vacuo* and the residual oil partitioned between ethyl acetate (50mL) and 1M hydrochloric acid (35mL). The ethyl acetate layer was separated, washed sequentially with saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica with 0-100% ethyl acetate in isohexane as eluant gave the desired compound (180 mg). ^{1}H NMR δ (d_6-DMSO): 1.28 (d, 6H), 2.74 (s, 3H), 4.74 (m, 1H), 6.86 (m, 1H), 7.20-7.33 (m, 4H), 7.50 (m, 1H), 7.53 (d, 1H), 7.72 (d, 2H), 12.62 (bs, 1H); *m/z* 417 $(M+H)^+$

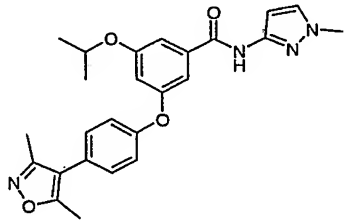
The following examples were synthesised in an analogous fashion:-

Example	Structure	*m/z*	NMR
5a		426 $(M+H)^+$ 424 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.28 (d, 6H), 2.86-2.98 (br s, 6H), 4.73 (m, 1H), 6.80 (m, 1H), 7.04 (m, 1H), 7.11-7.20 (m, 2H), 7.27 (m, 2H), 7.47 (m, 2H), 7.54 (d, 1H), 12.62 (s, 1H)
5b		415 $(M+H)^+$ 413 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.20 (t, 3H), 1.29 (d, 6H), 2.94 (m, 2H), 4.73 (m, 1H), 6.77 (m, 1H), 7.05 (d, 2H), 7.20 (m, 1H), 7.26 (m, 1H), 7.37 (d, 2H), 7.45 (s, 1H), 7.53 (d, 1H), amide NH not seen
5c[$]		423 $(M+H)^+$, 421 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 1.35 (d, 6H), 4.55 (m, 1H), 6.80 (m, 1H), 6.95 (m, 1H), 7.12 (d, 2H), 7.18 (m, 1H), 7.22 (m, 1H), 7.30 (m, 1H), 8.08 (d, 2H), 8.45 (s, 1H)

[$]Required further chromatography, eluting with 0-2% methanol in dichloromethane.

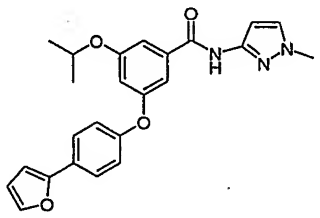
The synthesis of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide is described in Example 1 above.

Example 6: 3-[4-(3,5-Dimethylisoxazol-4-yl)phenoxy]-5-(1-methylethyl)oxy-N-(1-methyl-1H-pyrazol-3-yl)benzamide



To a stirred solution of 3-{[4-(3,5-dimethylisoxazol-4-yl)phenyl]oxy}-5-[(1-methylethyl)oxy] benzoic acid (0.3 mmol) in dichloromethane (2 mL) was added oxalyl chloride (50 µl) and a drop of DMF. The reaction was stirred overnight at room temperature, then evaporated in *vacuo*. The resulting acid chloride was dissolved in dichloromethane (1 mL), and added to a solution of 1-methyl-1*H*-pyrazol-3-amine (0.38 mmol) and diisopropylethylamine (0.9 mmol) in dichloromethane (2 mL). The reaction was stirred at room temperature for 48 hours. The reaction mixture was diluted with dichloromethane, and washed twice with 2M hydrochloric acid, then with saturated aqueous sodium hydrogen carbonate and brine. The solution was dried ($MgSO_4$), filtered, and evaporated to yield the product (84% yield). ^{1}H NMR δ ($CDCl_3$): 1.35 (d, 6H), 2.30 (s, 3H), 2.40 (s, 3H), 3.80 (s, 3H), 4.60 (m, 1H), 6.75 (m, 1H), 6.80 (m, 1H), 7.10 (m, 3H), 7.25 (br m, 4H), 8.70 (br s, 1H); *m/z* 447 $(M+H)^+$

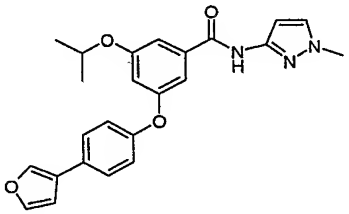
Example 7: 3-[(4-Furan-2-ylphenyl)oxy]-5-(1-methylethyl)oxy-N-(1-methyl-1H-pyrazol-3-yl)benzamide



To a stirred solution of 3-[(4-furan-2-ylphenyl)oxy]-5-[(1-methylethyl)oxy]benzoic acid (0.26 mmol) in DMF (2 mL) was added *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.33 mmol). The resulting solution was stirred for 5 minutes at room temperature, and a solution of diisopropylethylamine (0.65 mmol) and 1-methyl-1*H*-pyrazol-3-amine (0.31 mmol) in DMF (1 mL) added. The reaction was stirred overnight at room temperature, and evaporated in *vacuo*. The crude material was dissolved in ethyl acetate, and washed twice with 2M hydrochloric acid then 2M sodium hydroxide and brine. The solution

was dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica with 10-60% ethyl acetate in isohexane as eluant to give the desired product (86% yield). ^{1}H NMR δ ($CDCl_3$): 1.35 (d, 6H), 3.75 (s, 3H), 4.55 (m, 1H), 6.45 (m, 1H), 6.60 (m, 1H), 6.70 (m, 1H), 6.80 (m, 1H), 7.00 (m, 3H), 7.15 (s, 1H), 7.27 (m, 1H), 7.45 (s, 1H), 7.65 (d, 2H), 8.60 (br s, 1H); *m/z* 418 $(M+H)^+$

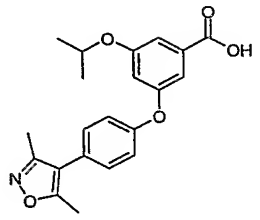
Example 8: 3-[(4-Furan-3-ylphenyl)oxy]-5-[(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide



In a similar fashion to that described above for Example 7, 3-[(4-furan-3-ylphenyl)oxy]-5-[(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide, was prepared from the corresponding acid. ^{1}H NMR δ ($CDCl_3$): 1.35 (d, 6H), 3.75 (s, 3H), 4.55 (m, 1H), 6.65 (s, 1H), 6.70 (m, 1H), 6.80 (m, 1H), 6.98 (s, 1H), 7.02 (d, 2H), 7.12 (s, 1H), 7.25 (m, 1H), 7.45 (m, 3H), 7.70 (s, 1H), 8.60 (br s, 1H); *m/z* 418 $(M+H)^+$

The requisite precursors for Examples 6-8 were prepared as described below:

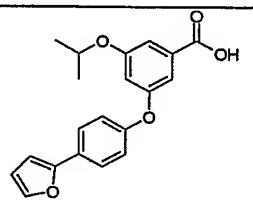
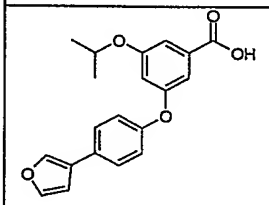
3-{[4-(3,5-Dimethylisoxazol-4-yl)phenyl]oxy}-5-[(1-methylethyl)oxy]benzoic acid



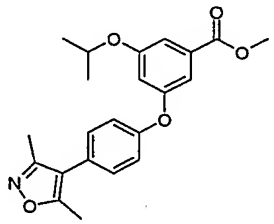
To a stirred solution of methyl 3-{[4-(3,5-dimethylisoxazol-4-yl)phenyl]oxy}-5-[(1-methylethyl)oxy]benzoate (0.31 mmol) in THF (2mL) was added lithium hydroxide (0.62 mmol) and water (0.35 mL). The reaction was stirred overnight at room temperature, before the addition of further lithium hydroxide (0.31 mmol) and water (0.2 mL). The reaction was stirred at room temperature for a further 3 hours, acidified with 2M hydrochloric acid and partitioned between water and ethyl acetate. The layers were separated and the aqueous layer re-extracted with ethyl acetate. The combined organic layers were washed with brine, dried [illegible]

1.35 (d, 6H), 2.30 (s, 3H), 2.45 (s, 3H), 4.60 (s, 1H), 6.85 (m, 1H), 7.10 (d, 2H), 7.22 (d, 2H), 7.35 (m, 1H), 7.40 (m, 1H); *m/z* 368 $(M+H)^+$, 366 $(M-H)^-$

The acids required for the synthesis of Example 7 and Example 8 were made using an analogous method:

Structure	NMR	*m/z*
	^{1}H NMR δ ($CDCl_3$): 1.35 (d, 6H), 4.55 (m, 1H), 6.45 (m, 1H), 6.60 (m, 1H), 6.80 (m, 1H), 7.05 (d, 2H), 7.30 (m, 1H), 7.35 (s, 1H), 7.45 (s, 1H), 7.65 (d, 2H)	339 $(M+H)^+$ 337 $(M-H)^-$
	^{1}H NMR δ ($CDCl_3$): 1.35 (d, 6H), 4.60 (m, 1H), 6.65 (m, 1H), 6.80 (m, 1H), 7.05 (d, 2H), 7.30 (m, 1H), 7.35 (m, 1H), 7.45 (m, 3H), 7.70 (s, 1H)	337 $(M-H)^-$

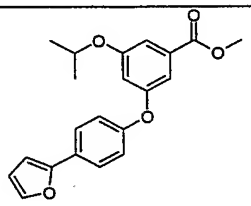
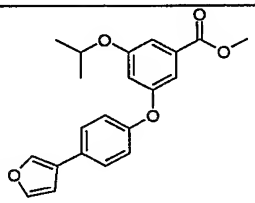
Methyl 3-{[4-(3,5-dimethylisoxazol-4-yl)phenyl]oxy}-5-[(1-methylethyl)oxy]benzoate



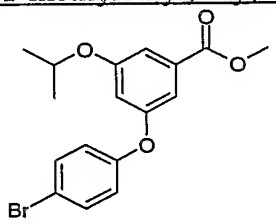
Methyl 3-[(4-bromophenyl)oxy]-5-[(1-methylethyl)oxy]benzoate (0.74 mmol) and 3,5-dimethylisoxazole-4-boronic acid (0.81 mmol) were suspended in a 1:1 mixture of dimethoxyethane and 2M sodium carbonate (6 mL). The mixture was degassed, before the addition of tetrakis(triphenylphosphine)palladium (0.015 mmol). The mixture was again degassed, and stirred at 80°C, then at room temperature overnight. The reaction was filtered through diatomaceous earth then evaporated in *vacuo*. The residual oil was partitioned between ethyl acetate and 2M sodium hydroxide. The ethyl acetate layer was separated, washed with brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica with 10% ethyl acetate in isohexane as eluant to give the desired ester (43% yield).

^{1}H NMR δ ($CDCl_3$): 1.35 (d, 6H), 2.25 (s, 3H), 2.45 (s, 3H), 3.90 (s, 3H), 4.60 (m, 1H), 6.80 (m, 1H), 7.10 (d, 2H), 7.25 (br m, 3H), 7.35 (br s, 1H); *m/z* 382 $(M+H)^+$

The esters required for the synthesis of Example 7 and Example 8 were prepared using an analogous method:

Structure	NMR	*m/z*
	^{1}H NMR δ ($CDCl_3$): 1.35 (d, 6H), 3.90 (s, 3H), 4.55 (m, 1H), 6.45 (m, 1H), 6.60 (m, 1H), 6.70 (m, 1H), 7.05 (d, 2H), 7.22 (m, 1H), 7.30 (m, 1H), 7.45 (s, 1H), 7.65 (d, 2H)	727 $(2M+Na)^+$
	^{1}H NMR δ ($CDCl_3$): 1.35 (d, 6H), 3.90 (s, 3H), 4.55 (m, 1H), 6.65 (s, 1H), 6.72 (m, 1H), 7.02 (d, 2H), 7.22 (m, 1H), 7.30 (m, 1H), 7.45 (m, 3H), 7.70 (s, 1H)	353 $(M+H)^+$

Methyl 3-[(4-bromophenyl)oxyl-5-[(1-methylethyl)oxy]benzoate



A solution of methyl 3-hydroxy-5-[(1-methylethyl)oxy]benzoate (0.024 mol), 4-bromophenyl boronic acid (0.048 mol), copper (II) acetate (0.048 mol), triethylamine (0.12 mol) and freshly activated 4Å molecular sieves (25 g) in dichloromethane (500 mL) was stirred at ambient temperature and under ambient atmosphere for 7 days. The reaction mixture was filtered, the dichloromethane removed *in vacuo*, and the residual oil partitioned between ethyl acetate and 2M hydrochloric acid. The ethyl acetate layer was separated, washed sequentially with saturated aqueous sodium hydrogen carbonate, brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica with 10-40% ethyl acetate in isohexane as eluant to give the desired ester (56% yield). ^{1}H NMR δ (d_6-DMSO): 1.25 (d, 6H), 3.80 (s,

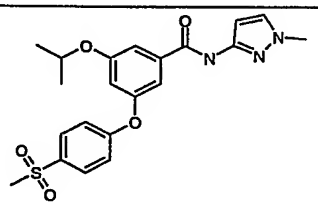
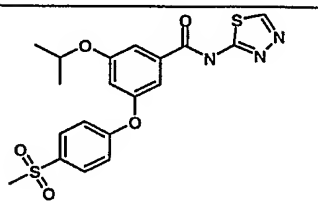
3H), 4.65 (m, 1H), 6.87 (m, 1H), 6.97 (m, 1H), 7.03 (d, 2H), 7.20 (m, 1H), 7.55 (d, 2H); *m/z* 367 $(M+H)^+$

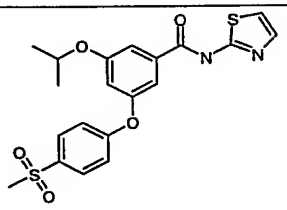
The synthesis of methyl 3-hydroxy-5-[(1-methylethyl)oxy]benzoate is described above in Example 1.

Example 9: General Procedure for Amide Synthesis – HATU Coupling

Diisopropylethylamine (2.5 equivalents) was added to a suspension of 3-{(1-methylethyl)oxy}-5-{[4-(methylsulfonyl)phenyl]oxy}benzoic acid (1 equivalent), *O*-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexofluorophosphate (1.25 equivalents) and amine (1.25 equivalents) in DMF (20mL). The initial suspension dissolved into a dark orange solution. The resulting mixture was stirred at ambient temperature for 2 hours. The DMF was removed *in vacuo,* and the residue azeotroped with toluene. Water was added and the mixture extracted with ethyl acetate. The extracts were combined and washed sequentially with 1M hydrochloric acid, saturated sodium hydrogen carbonate solution and brine. The solution was dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give the crude product which was chromatographed (50% ethyl acetate in isohexane) to give desired compound (40-70% yield).

Using the above method, **Examples 9a-9c** were prepared:-

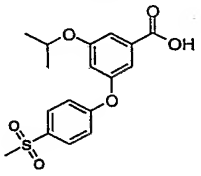
Example	Structure	*m/z*	NMR
9a		430 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.25 (d, 6H), 3.2 (s, 3H), 3.8 (s, 3H), 4.75 (m, 1H), 6.55 (d, 1H), 6.85 (s, 1H), 7.2 (d, 2H), 7.3 (s, 1H), 7.45 (s, 1H), 7.6 (d, 1H), 7.9 (d, 2H), 10.85 (br s, 1H)
9b		434 $(M+H)^+$ 432 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.25 (d, 6H), 3.2 (s, 3H), 4.75 (m, 1H), 7.0 (s, 1H), 7.2 (d, 2H), 7.4 (s, 1H), 7.6 (s, 1H), 7.95 (d, 1H), 9.2 (s, 1H), 13.10 (br s, 1H)

9c#		433 $(M+H)^+$, 431 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 3.2 (s, 3H), 4.75 (m, 1H), 7.0 (s, 1H), 7.2 (d, 2H), 7.25 (s, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 7.65 (s, 1H), 7.95 (d, 1H)

#Example 9c may be crystallised by allowing isohexane to vapour diffuse into a solution of the compound in ethylacetate, in a closed system, with subsequent slow evaporation of the mixture at room temperature over 4 days, mpt 145-147°C

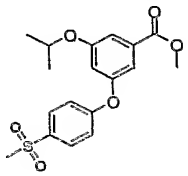
The required acid for the synthesis of Examples 9a-9c was prepared as described below:-

3-{(1-Methylethyl)oxy}-5-{[4-(methylsulfonyl)phenyl]oxy}benzoic acid



A solution of methyl 3-{(1-methylethyl)oxy}-5-{[4-(methylsulfonyl)phenyl]oxy}benzoate (15.1 mmol) in THF (90 mL) was treated with a solution of 1M sodium hydroxide (37 mmol), and the reaction mixture stirred for 13 hours at ambient temperature. Most of the organic solvent was removed *in vacuo,* and the remaining solution was diluted with water (50 mL). The resulting aqueous solution was acidified to pH4 with 1M citric acid solution, and extracted with ethyl acetate (2 x 40 mL). The extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated to give the desired compound (82% yield). ^{1}H NMR δ (d_6-DMSO): 1.25 (d, 3H), 3.2 (s, 3H), 4.64 (m, 1H), 6.95 (s, 1H), 7.06 (s, 1H), 7.2(d, 2H), 7.25 (s, 1H), 7.95 (d, 2H); *m/z* 349 $(M-H)^-$

Methyl 3-{(1-methylethyl)oxy}-5-{[4-(methylsulfonyl)phenyl]oxy}benzoate



A suspension of methyl 3-hydroxy-5-[(1-methylethyl)oxy]benzoate (24 mmol), boronic acid (1.1 equivalents), copper (II) acetate (1.1 equivalents), triethylamine (5 equivalents) and freshly activated 4 Å molecular sieves (31 g) in dichloromethane (250 mL) was stirred at

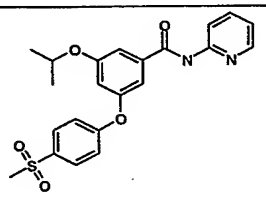
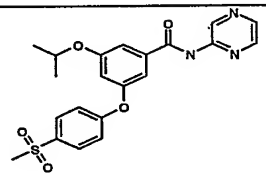
ambient temperature and under ambient atmosphere for 2 days. The reaction mixture was filtered, the dichloromethane removed *in vacuo* and the residual oil partitioned between ethyl acetate and 1-2M hydrochloric acid. The ethyl acetate layer was separated, washed with aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica (with 10-40% ethyl acetate in isohexane as eluant) to give the desired ester (64% yield). ^{1}H NMR δ (d_6-DMSO): 1.25 (d, 3H), 3.2 (s, 3H), 4.64 (m, 1H), 6.95 (s, 1H), 7.06 (s, 1H), 7.2(d, 2H), 7.25 (s, 1H), 7.95 (d, 2H); *m/z* 365 $(M+H)^+$

The synthesis of methyl 3-hydroxy-5-[(1-methylethyl)oxy]benzoate is described above in Example 1.

Example 10: General Procedure for Amide Synthesis – Phosphorus Oxychloride Coupling

Phosphorus oxychloride (0.75mmol; 1.5 equivalents) was added dropwise to a stirred solution of 3-{(1-methylethyl)oxy}-5-{[4-(methylsulfonyl)phenyl]oxy}benzoic acid (0.5mmol) and the appropriate amino azine (1.25 equivalents) in pyridine (5mL). The resulting mixture was stirred at ambient temperature for 4 hours. The pyridine was removed *in vacuo,* and the residue taken up in ethyl acetate. The mixture was washed sequentially with water, 1M citric acid and brine, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give the crude product, which was chromatographed (eluing with 30-90% ethyl acetate in isohexane) to give the desired product (~20% yield).

Using the above method, **Examples 10a & 10b** were prepared:-

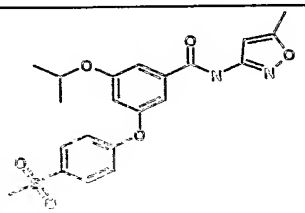
Example	Structure	*m/z*	NMR
10a		427 $(M+H)^+$ 425 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.25 (d, 6H), 3.2 (s, 3H), 4.75 (m, 1H), 6.9 (s, 1H), 7.15 (m, 1H), 7.2 (d, 2H), 7.3 (s, 1H), 7.5 (s, 1H), 7.8 (app t, 1H), 7.95 (d, 2H), 8.15 (d, 1H), 8.4 (d, 1H), 10.8 (br s, 1H)
10b		428 $(M+H)^+$ 426 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.25 (d, 6H), 3.2 (s, 3H), 4.75 (m, 1H), 6.95 (s, 1H), 7.2 (d, 2H), 7.35 (s, 1H), 7.5 (s, 1H), 7.95 (d, 2H), 8.4 (d, 1H), 8.45 (d, 1H), 9.4 (d, 1H), 11.15 (br s, 1H)

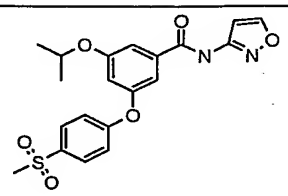
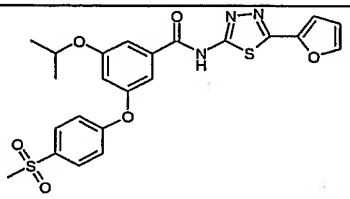
The synthesis of 3-{(1-methylethyl)oxy}-5-{[4-(methylsulfonyl)phenyl]oxy}benzoic acid is described in Example 9 above.

Example 11: General Procedure for Amide Synthesis – Oxalyl Chloride Coupling

To a stirred solution of 3-{(1-methylethyl)oxy}-5-{[4-(methylsulfonyl)phenyl]oxy}benzoic acid (0.285mmol) in dry dichloromethane (2mL), was added, dropwise under argon, oxalyl chloride (2 equivalents) and DMF (1 drop). The resulting solution was stirred at ambient temperature for 1-2 hrs. The solvent was removed *in vacuo* and the crude mixture taken up in pyridine (2mL) and added to the appropriate amine (2.2 equivalents). The reaction mixture was stirred at room temperature, or heated if necessary, and monitored by TLC and/or LCMS. The pyridine was removed *in vacuo,* and water and ethyl acetate added. The organic layer was washed sequentially with 1M citric acid and brine solution and dried ($MgSO_4$), concentrated *in vacuo,* and the residue chromatographed on silica (eluting with 30-90% ethyl acetate in isohexane) to give the desired product (typically 35-40% yield).

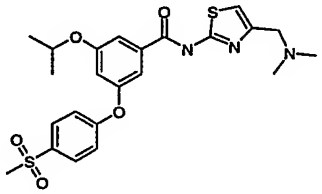
In a similar manner, **Examples 11a-11c** were prepared:-

Example	Structure	*m/z*	NMR
11a		431 $(M+H)^+$ 429 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 1.25 (d, 6H), 2.4 (s, 3H), 3.2 (s, 3H), 4.75 (m, 1H), 6.7 (s, 1H), 6.95 (s, 1H), 7.2 (d, 2H), 7.3 (s, 1H), 7.45 (s, 1H), 7.9 (d, 2H), 11.3 (br s, 1H)

11b		417 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.30 (dd, 6H), 3.23 (s, 3H), 4.78 (sept, 1H), 6.96 (s, 1H), 7.03 (s, 1H), 7.25 (d, 2H), 7.32 (s, 1H), 7.50 (s, 1H), 7.96 (d, 2H), 8.87 (s, 1H), 11.46 (s, 1H)
11c		500 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.33 (d, 6H), 3.23 (s, 3H), 4.78 (m, 1H), 6.77 (d, 1H), 7.01 (t, 1H), 7.26 (m, 3H), 7.42 (s, 1H), 7.60 (s, 1H), 7.98 (m, 3H), 13.22 (s, 1H)

The synthesis of 3-{(1-methylethyl)oxy}-5-{[4-(methylsulfonyl)phenyl]oxy}benzoic acid is described in Example 9 above.

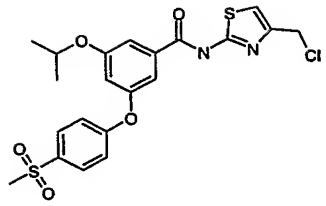
Example 12: N-{4-[(Dimethylamino)methyl]-1,3-thiazol-2-yl}-3-(1-methylethyl)oxy-5-[4-(methylsulfonyl)phenoxy]benzamide



To a solution of N-{4-chloromethyl-1,3-thiazol-2-yl}-3-(1-methylethyl)oxy-5-[4-(methylsulfonyl)phenoxy]benzamide (1.0mmol) in THF (4mL) was added dimethylamine in THF (10mL of a 2M solution) and stirred at ambient temperature for 13 hours. The reaction mixture was concentrated *in vacuo* and the residue taken up in ethyl acetate. The mixture was washed sequentially with 1M sodium hydroxide and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (eluting with 20-80% ethyl acetate in isohexane) to give the desired compound (15% yield). ^{1}H NMR δ (d_6-DMSO): 1.3 (d, 6H), 2.2 (s, 6H), 3.2 (s, 3H), 3.4 (s, 2H), 4.75 (m, 1H), 6.9 (s, 1H), 7.0 (s, 1H), 7.2 (d, 2H), 7.35 (s, 1H), 7.55 (s, 1H), 7.95 (d, 1H); *m/z* 490 $(M+H)^+$, 488 $(M-H)^-$

The required chloromethylthiazole for Example 12 was prepared as described below:

N-{4-Chloromethyl-1,3-thiazol-2-yl}-3-(1-methylethyl)oxy-5-[4-(methylsulfonyl) phenoxy]benzamide



To a stirred solution of 3-{(1-methylethyl)oxy}-5-{[4-(methylsulfonyl)phenyl]oxy}benzoic acid (1.0mmol) in dichloromethane (10mL) was added 1 drop of DMF and oxalyl chloride (2.0mmol; 2.0 equivalents) dropwise, and the resulting mixture stirred at ambient temperature under argon for 2 hours. The reaction mixture was concentrated *in vacuo* and azeotroped with dichloromethane. The residue was dissolved in dichloromethane and 4-chloromethylthiazol-2-ylamine (1.0mmol) in dichloromethane, diisopropylethylamine (2.5mmol) and dimethylaminopyridine (0.1 mmol) added. The resulting mixture was stirred for 13 hours under argon at ambient temperature. The reaction was concentrated *in vacuo,* and chromatographed (eluting with 50-60% ethyl acetate in isohexane) to give the desired compound (53% yield). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 6H), 2.2 (s, 6H), 3.2 (s, 3H), 3.4 (s, 2H), 4.75 (m, 1H), 6.9 (s, 1H), 7.0 (s, 1H), 7.2 (d, 2H), 7.35 (s, 1H), 7.55 (s, 1H), 7.95 (d, 1H)

The synthesis of 3-{(1-Methylethyl)oxy}-5-{[4-(methylsulfonyl)phenyl]oxy}benzoic acid is described above in Example 9.

BIOLOGICAL

Tests:

The biological effects of the compounds of formula (I) may be tested in the following way:

(1) Enzymatic activity

Enzymatic activity of recombinant human pancreatic GLK may be measured by incubating GLK, ATP and glucose. The rate of product formation may be determined by coupling the assay to a G-6-P dehydrogenase, NADP/NADPH system and measuring the increase in optical density at 340nm (Matschinsky et al 1993).

Production of recombinant GLK and GLKRP:

Human GLK and GLKRP cDNA was obtained by PCR from human pancreatic and hepatic mRNA respectively, using established techniques described in Sambrook J. Fritsch EF

& Maniatis T, 1989. PCR primers were designed according to the GLK and GLKRP cDNA sequences shown in Tanizawa et al 1991 and Bonthron, D.T. *et al* 1994 (later corrected in Warner, J.P. 1995).

Cloning in Bluescript II vectors

GLK and GLKRP cDNA was cloned in E. coli using pBluescript II, (Short et al 1998) a recombinant cloning vector system similar to that employed by Yanisch-Perron C *et al* (1985), comprising a colEI-based replicon bearing a polylinker DNA fragment containing multiple unique restriction sites, flanked by bacteriophage T3 and T7 promoter sequences; a filamentous phage origin of replication and an ampicillin drug resistance marker gene.

Transformations

E. Coli transformations were generally carried out by electroporation. 400 mL cultures of strains DH5a or BL21(DE3) were grown in L-broth to an OD 600 of 0.5 and harvested by centrifugation at 2,000g. The cells were washed twice in ice-cold deionised water, resuspended in 1mL 10% glycerol and stored in aliquots at -70^{0}C. Ligation mixes were desalted using Millipore V series™ membranes (0.0025mm) pore size). 40mL of cells were incubated with 1mL of ligation mix or plasmid DNA on ice for 10 minutes in 0.2cm electroporation cuvettes, and then pulsed using a Gene Pulser™ apparatus (BioRad) at 0.5kVcm^{-1}, 250mF. Transformants were selected on L-agar supplemented with tetracyline at 10mg/mL or ampicillin at 100mg/mL.

Expression

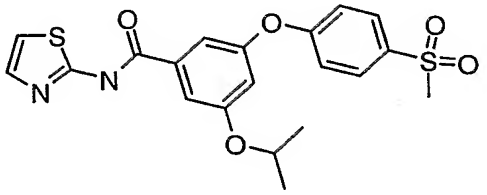
GLK was expressed from the vector pTB375NBSE in E.coli BL21 cells,, producing a recombinant protein containing a 6-His tag immediately adjacent to the N-terminal methionine. Alternatively, another suitable vector is pET21(+)DNA, Novagen, Cat number 697703. The 6-His tag was used to allow purification of the recombinant protein on a column packed with nickel-nitrilotriacetic acid agarose purchased from Qiagen (cat no 30250).

GLKRP was expressed from the vector pFLAG CTC (IBI Kodak) in E.coli BL21 cells, producing a recombinant protein containing a C-terminal FLAG tag. The protein was purified initially by DEAE Sepharose ion exchange followed by utilisation of the FLAG tag for final

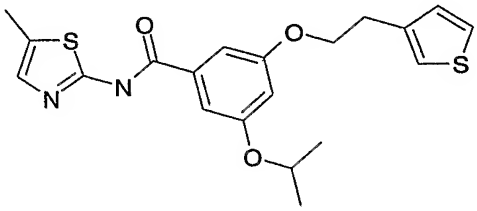
purification on an M2 anti-FLAG immunoaffinity column purchased from Sigma-Aldrich (cat no. A1205).

(2) Oral Glucose Tolerance Test (OGTT)

Oral glucose tolerance tests were done on conscious Zucker obese fa/fa rats (age 12-13 weeks or older) fed a high fat diet (45 % kcal fat) for at least two weeks prior to experimentation. The animals were fasted for 2 hours before use for experiments. A test compound or a vehicle was given orally 120 minutes before oral administration of a glucose solution at a dose of 2 g/kg body weight. Blood glucose levels were measured using a Accucheck glucometer from tail bled samples taken at different time points before and after administration of glucose (time course of 60 minutes). A time curve of the blood glucose levels was generated and the area-under-the-curve (AUC) for 120 minutes was calculated (the time of glucose administration being time zero). Percent inhibition is determined using the AUC in the vehicle-control group as zero percent inhibition.



Example 9c



Example II107

Compounds of the invention generally have an activating activity for glucokinase with an EC_{50} of less than about 500nM. For example, Example 9c has an EC_{50} of 50nM.

Example 9c and Example II107 in WO 03/015774 have broadly similar EC_{50} values. However Example 9c has superior oral exposure and exhibits 18% OGTT activity at 10 mg/kg but Example II107 in WO 03/015774 is not active at 10 mg/kg.

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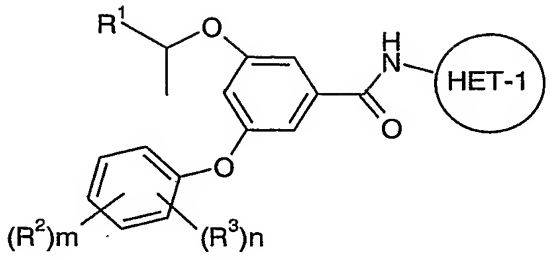
Claims:

1. A compound of Formula (I):



(I)

wherein:

R^1 is selected from methyl;

R^2 is selected from $-C(O)NR^4R^5$, $-SO_2NR^4R^5$, $-S(O)_pR^4$ and HET-2;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^6;

HET-2 is a 4-, 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- , and wherein a sulphur atom in the heterocyclic ring may optionally be oxidised to an S(O) or $S(O)_2$ group, which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^7;

R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano;

R^4 is selected from hydrogen, (1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from HET-2, $-OR^5$, $-SO_2R^5$, (3-6C)cycloalkyl (optionally substituted with 1 group selected from R^7) and $-C(O)NR^5R^5$] and HET-2;

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a heterocyclyl ring system as defined by HET-3;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl and HET-4;

R^7 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-3 is an N-linked, 4 to 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to an S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an N-linked, 7 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further heteroatom (in addition to the linking N atom) independently selected from O, S and N, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- group and wherein a sulphur atom in the ring may optionally be oxidised to an S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 substituents independently selected from R^8; or

HET-3 is an 6-10 membered bicyclic saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further nitrogen atom (in addition to the linking N atom) wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-; which ring is optionally substituted on an available carbon or nitrogen atom by 1 substituent selected from R^3;

R^8 is selected from $-OR^5$, (1-4C)alkyl, -C(O)(1-4C)alkyl, $-C(O)NR^4R^5$, (1-4C)alkylamino, di(1-4C)alkylamino, HET-3 (wherein said ring is unsubstituted), (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and $-S(O)pR^5$;

HET-4 is a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S;

p is (independently at each occurrence) 0, 1 or 2;

m is 0 or 1;

n is 0, 1 or 2;

provided that when m is 0, then n is 1 or 2;

or a salt, pro-drug or solvate thereof.

2. A compound of the formula (I) as claimed in Claim 1, or a salt, pro-drug or solvate thereof, wherein HET-1 is a 5-membered ring.

3. A compound of the formula (I) as claimed in Claim 1 or Claim 2, or a salt, pro-drug or solvate thereof, wherein HET-3 is a 4- to 6-membered ring.

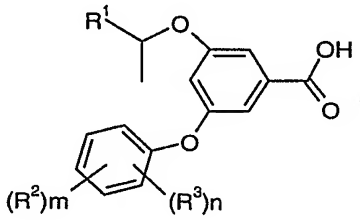
4. A pharmaceutical composition comprising a compound according to Claim 1, or a salt, pro-drug or solvate thereof, together with a pharmaceutically acceptable diluent or carrier.

5. A compound according to Claim 1 for use in the preparation of a medicament for treatment of a disease mediated through GLK.

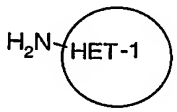
6. A method of treating GLK mediated diseases by administering an effective amount of a compound of Formula (I) as claimed in Claim 1 or salt, solvate or pro-drug thereof, to a mammal in need of such treatment.

7. A process for the preparation of a compound of Formula (I) as claimed in Claim 1, which comprises (wherein variables are as defined in Claim 1 unless otherwise stated):

(a) reaction of an acid of Formula (III) or activated derivative thereof with a compound of Formula (IV),



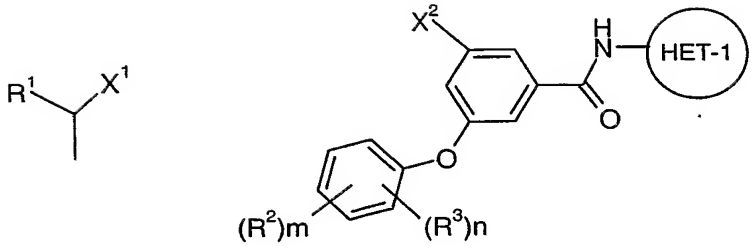
(III)



(IV);

or

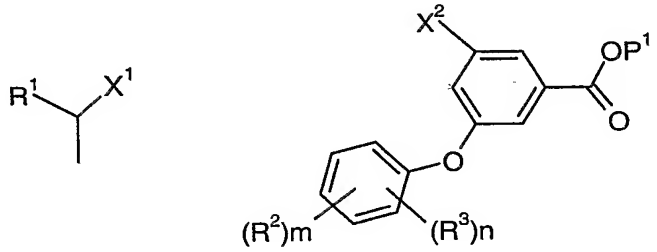
(b) reaction of a compound of Formula (V) with a compound of Formula (VI),



(V) (VI)

wherein X^1 is a leaving group and X^2 is a hydroxyl group or X^1 is a hydroxyl group and X^2 is a leaving group;

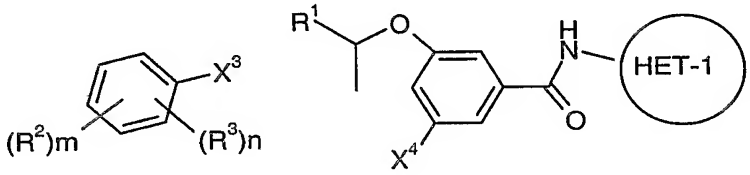
[or by reaction with the intermediate ester Formula (VII), wherein P^1 is a protecting group followed by ester hydrolysis and amide formation];



(V) (VII)

or

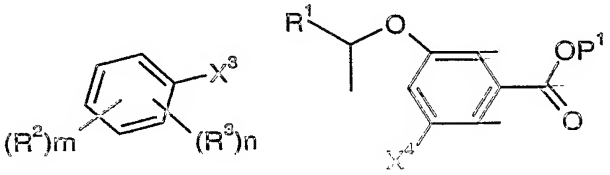
(c) reaction of a compound of Formula (VIII) with a compound of Formula (IX)



(VIII) (IX)

wherein X^3 is a leaving group or an organometallic reagent and X^4 is a hydroxyl group or X^3 is a hydroxyl group and X^4 is a leaving group or an organometallic reagent;

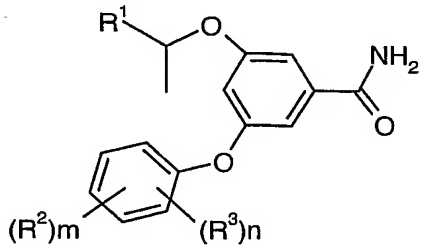
[or by reaction or (VIII) with the intermediate ester Formula (X), followed by ester hydrolysis and amide formation];



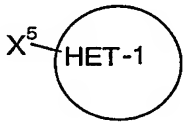
(VIII) (X)

or

(d) reaction of a compound of Formula (XI) with a compound of Formula (XII),



(XI)



(XII);

wherein X^5 is a leaving group;

and thereafter, if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a salt, pro-drug or solvate.